RISK OF ADOLESCENT DEPRESSION IN YOUTH WITH ADHD: A LONGITUDINAL TWIN INVESTIGATION

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To my mother

ABSTRACT

Objective: In two studies, this dissertation aimed to evaluate the robustness of the association between ADHD and depression, and to elucidate its etiology. Study I examined the predictive association between childhood ADHD and adolescent depression, and also between childhood ADHD and adolescent suicidality. The study investigated methodological explanations for the co-occurrence between ADHD and depression and tested whether the association between childhood ADHD and adolescent depression is attributable to rater bias effects, or is a consequence of shared comorbidity with conduct disorder. Study I also examined psychosocial factors and evaluated whether conflict with parents, academic underperformance, and victimization by peers mediate the association between childhood ADHD and adolescent depression. Study II examined the etiology of the relationship between ADHD and depression by estimating the magnitude of the genetic and environmental contributions to the co-occurrence between the two disorders. **Method:** Both studies were conducted in a population-based twin sample enriched with children with disruptive disorders and consisting of 998 twins. The participants were followed up in three multi-source structured diagnostic assessments, spanning 11 to 17 years of age. Study I hypotheses were tested using generalized linear models within a complex samples framework to account for the study's recruitment strategy and allow generalization of the results to the population. Study II utilized biometric modeling and incorporated sampling weights to take into consideration the oversampling of disruptive disorders. **Results:** The studies yielded four primary findings. First, symptoms of ADHD at age 11 years predicted depression that developed between the ages 11 and 17 years, and the prospective relationship between childhood ADHD and adolescent depression was not attributable to rater bias effects or conduct problems. A non-significant trend was suggestive of greater risk of depression associated with ADHD in females than males. Second, the co-occurrence between ADHD and depression was governed by shared

genetic factors operating either directly or indirectly via gene-environment correlations or interactions. Third, symptoms of ADHD at age 11 years predicted suicide attempts and suicidal ideation experienced through age 17, but the association with suicide attempts could be accounted for by the degree of conduct disorder symptomatology. Fourth, exposure to conflict with parents, and for girls only, bullying by peers, partly accounted for the association between childhood ADHD and adolescent depression. **Conclusions:** The present findings provided novel and important insights into the risk of psychopathology associated with ADHD. The results indicated that childhood ADHD was a robust predictor of adolescent depression. The etiology of the relationship was primarily genetic, although the mediation of risk is at least in part environmental. The findings highlight the need for depression screening in youth with ADHD and expansion of preventative intervention.

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GENERAL INTRODUCTION

ADHD is typically conceptualized as a behavioral syndrome and part of the childhood externalizing spectrum disorders. But the comorbidity between ADHD and oppositional defiant disorder and conduct disorder has overshadowed another important comorbidity, that between ADHD and depression. Meta-analytic evidence indicates that the odds of depression for community children and adolescents with ADHD are 5.5 times higher than the odds of depression for ADHD-free youth, with depression rates ranging between 12% and 50% (Angold, Costello, & Erkanli, 1999). Even higher rates of depression have been reported in clinically-referred youth with ADHD (Spencer, Biederman, & Wilens, 1999). Recent epidemiological surveys provide additional evidence for elevated risk of depression among youth with ADHD (Chen et al., 2013; Larson, Russ, Kahn, & Halfon, 2011; Smalley et al., 2007; Sonnby, Åslund, Leppert, & Nilsson, 2011). Additionally, prospective studies involving clinical samples have shown that youth with ADHD are more likely to experience suicidal ideation and attempt suicide (Barkley & Fischer, 2005; Biederman, Ball, et al., 2008; Chronis-Tuscano et al., 2010), although population based investigations are needed to further substantiate the findings (Impey & Heun, 2012).

Despite a growing literature documenting the co-occurrence of ADHD and depression, the etiology of the association has received little empirical attention, and thus our knowledge of the development of depressive pathology in youth with ADHD is correspondingly limited. Moreover, the literature is dominated by studies involving clinical, predominantly male samples which constrains generalizability and precludes evaluation of gender effects.

Previous studies have shown evidence of substantial familial co-aggregation of ADHD and depression, with first-degree relatives of probands with ADHD having elevated rates of depression (Chronis et al., 2003; Faraone & Biederman, 1997; Nigg & Hinshaw, 1998). However, with very few exceptions (J. Cole, Ball, Martin, Scourfield, & McGuffin, 2009; Sprich,

Biederman, Crawford, Mundy, & Faraone, 2000), prior research has relied on traditional family designs which preclude firm conclusions about causal influences underlying family associations as environmental and genetic forces are confounded within families. Consequently, genetically informative studies are needed to disambiguate genetic effects from environmental influences on the co-occurrence between ADHD and depression. The only twin study to date that explicitly examined the comorbidity between ADHD and depression concluded that the overlap between the two disorders is governed by shared genetic factors operating either directly, or indirectly via gene-environment correlations or interactions (J. Cole et al., 2009). Nevertheless, methodological limitations such as exclusive reliance on parent ratings of child psychopathology prevent conclusive interpretation of the results.

It is possible that ADHD increases exposure to environmental hazards which in turn predispose to later depression, consistent with a gene-environment correlation effect. An extensive literature has documented that ADHD is associated with a multitude of stressors and negative outcomes, including conflict with parents (Johnston & Mash, 2001), academic underachievement (Loe & Feldman, 2007) and poor interpersonal functioning (McQuade & Hoza, 2008). Nevertheless, few studies have examined these factors as they relate to depression in youth with ADHD and the findings have been mixed (e.g., Biederman et al., 2008; Drabick, Gadow, & Sprafkin, 2006; Ostrander & Herman, 2006). Importantly, longitudinal investigations are needed when examining potential factors mediating the association between ADHD and depression as cross-sectional studies do not allow strong inferences because premorbid characteristics present before the onset of depression are confounded with adverse effects of depression and thus the direction of the effect cannot be clearly established.

The paucity of studies investigating the co-occurrence between ADHD and depression may be explained in part by the possibility that the nature of the association is epiphenomenal or

artifactual. It has been contended that the relationship between ADHD and depression is an epiphenomenon related to conduct disorder, in other words attributable to the comorbidity of each of the disorders with conduct disorder (Angold et al., 1999). The few studies examining whether conduct disorder accounts for the association between ADHD and depression have been methodologically disparate and have yielded mixed findings thus not affording firm conclusions (Blackman, Ostrander, & Herman, 2005; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Meinzer et al., 2013). Also, rater bias may lead to spurious associations between ADHD and depression, given that depressed mothers tend to rate their children's symptoms as more severe than is objectively warranted (Chi & Hinshaw, 2002; Chilcoat & Breslau, 1997), yet population-based studies have relied almost exclusively on single reporters of child psychopathology.

As a result, there is an important need in the literature to elucidate the underpinnings of the association between ADHD and depression. The present studies had two specific aims. The first aim was to assess the robustness of the association between childhood ADHD and adolescent depression. By submitting the relationship to rigorous empirical scrutiny to exclude the possibility that it reflects an ephiphenomenal or artifactual association, I hoped to place the co-occurrence between ADHD and depression on firm empirical ground, and thus spur new inquiries into the etiological processes responsible for the heightened risk of depression among youth with ADHD. The second aim was to illuminate the etiology of the association between ADHD and depression. Because the present studies examined the relationship between the two pathologies through a genetically informative lens and using a longitudinal design, they should permit for stronger conclusions about the genetic architecture of the co-occurrence and more compelling identification of factors mediating the association.

To achieve these objectives, two studies were conducted in a population-based twin sample (520 girls and 478 boys) enriched with children with disruptive disorders, followed from

age 11 to age 17 years. The first study sought to examine the predictive association between ADHD at age 11 and depression developed between 11 and 17 years of age, and also between ADHD at age 11 and suicidal ideation and suicide attempts by age 17 years, while taking into account rater bias effects and the influence of conduct disorder. Additionally, the first study sought to assess the possible mediating roles of parent-child conflict, academic difficulties, and victimization by peers in the association between childhood ADHD and adolescent depression. The second study sought to estimate the magnitude of the genetic and environmental influences impacting the association between childhood ADHD and adolescent depression using biometric modeling.

The present studies should contribute to elucidate the mechanisms underlying the association between ADHD and depression. Such results could also have ample clinical implications, informing early identification of children at risk for depression and suicidal behavior and promoting proactive intervention.

Chapter 1 STUDY I

1.1 INTRODUCTION

A growing body of evidence demonstrates a high rate of comorbidity between attention-deficit hyperactivity disorder (ADHD) and major depressive disorder among children and adolescents. Meta-analytic evidence indicates that 12% to 50% of community children and adolescents with ADHD have comorbid depression (Angold et al., 1999). More recent research involving epidemiological (Chen et al., 2013; Larson et al., 2011; Lingineni et al., 2012; Smalley et al., 2007; Sonnby et al., 2011), community (Blackman et al., 2005; Meinzer et al., 2013) and clinical samples (Biederman et al., 2006; Biederman, Ball, et al., 2008; Chronis-Tuscano et al., 2010; Lahey et al., 2007; Staikova, Marks, Miller, Newcorn, & Halperin, 2010) has confirmed elevated rates of depression in youth with ADHD. The comorbidity between ADHD and depression has also been shown in adults, with epidemiological surveys demonstrating that adult ADHD is associated with approximately three-fold increase in odds for depression (Kessler et al., 2006; Zwaan et al., 2011).

Moreover, prospective studies have shown that children and adolescents with ADHD are more likely to experience suicidal ideation and to attempt suicide through adolescence and early adulthood than controls (Barkley & Fischer, 2005; Biederman, Ball, et al., 2008; Chronis-Tuscano et al., 2010; Hinshaw et al., 2012). However, these studies involved primarily clinically ascertained children and adolescents, potentially with more severe psychopathology, thus the possibility of clinical referral bias contributing to the findings cannot be excluded. A recent review of the relationship between ADHD and suicidality concluded that ADHD is associated with elevated risk to self, but the authors cautioned that the literature on this topic, while growing, remains limited, and highlighted the need for population based investigations (Impey & Heun, 2012). These findings underscore the need for prospective population based studies to further our

understanding of depression that emerges in youth with ADHD in order to inform early identification of at-risk children and promote proactive intervention, especially given that ADHD almost always precedes depression (Kessler et al., 2005).

The nature of the association between ADHD and depression has been debated. It has been advanced that it illustrates an epiphenomenon, a secondary association stemming from the comorbidity of each of the disorders with conduct disorder (Angold et al., 1999). An abundant literature documents that ADHD is associated with conduct disorder (e.g., Nock, Kazdin, Hiripi, & Kessler, 2006; Smalley et al., 2007) and that a substantial minority of youth with conduct disorder has depression (Marmorstein & Iacono, 2003). Clinical and population-based studies that examined whether the link between the ADHD and depression is explained by conduct disorder have yielded mixed findings. A number of studies have reported a robust association, independent of conduct disorder (Biederman, Ball, et al., 2008; Blackman et al., 2005; Meinzer et al., 2013), while some studies have indicated that that the association disappeared when taking into account the overlap between ADHD and conduct disorder (Costello et al., 2003; Hinshaw, Owens, Sami, & Fargeon, 2006; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998). Divergent analytical approaches, recruitment practices (e.g., reliance on male clinical samples), assessment procedures and variations in age at assessment may have contributed to the inconsistent findings. Resolving the issue of whether ADHD predicts later depression when taking conduct disorder into consideration is important in order to clarify the role of ADHD in the developmental pathway resulting in depression, and to help determine whether ADHD may be an appropriate target for interventions aiming to prevent depression in adolescence.

Rater effects are additional factors that warrant careful consideration when examining the co-occurrence between ADHD and depression, given their potential for confounding and obscuring the association. Children and adolescents underestimate the extent of their ADHD

symptoms (Hope et al., 1999; Loeber, Green, Lahey, & Stouthamer-Loeber, 1991), which highlights the importance of multi-source assessment of ADHD. Mothers are reliable reporters of child psychopathology, have the advantage of observing the child under a variety of circumstances (and for extended periods of time), and are most consistently available to report on the children's symptoms (Faraone, Biederman, & Milberger, 1995). But maternal report can be a source of bias if the mother is depressed. The depression-distortion hypothesis posits that the ratings of a child's behavior are negatively biased by the rater's depressed mood (Richters, 1992). The depression-distortion hypothesis has been frequently investigated, typically by examining the association between maternal depressive symptoms and the discrepancy between maternal ratings of child behavior and ratings provided by other reporters (e.g., teacher).

The empirical support for maternal over-reporting of ADHD symptoms and disruptive behaviors is generally consistent (Najman et al., 2000; Youngstrom, Izard, & Ackerman, 1999; Youngstrom, Loeber, & Stouthamer-Loeber, 2000) and includes investigations involving large population-based samples (Boyle & Pickles, 1997; Fergusson, Lynskey, & Horwood, 1993), although there are some exceptions (e.g., Baumann, Pelham, Lang, Jacob, & Blumenthal, 2004). Additionally, research shows that the maternal depression distortion also extends to child internalizing psychopathology. Depressed mothers tend to over-report children's depressive symptoms (Briggs-Gowan, Carter, & Schwab-Stone, 1996; Youngstrom et al., 2000), although evidence from a study involving a nationally representative sample and investigating child internalizing symptoms suggests that the magnitude of the rating bias associated with maternal depressive symptoms is modest (Toorn et al., 2009). Thus, the depressed mothers' tendency to overstate their children's ADHD and depressive symptoms, together with the fact that offspring of depressed mothers have elevated rates of depression could lead to an overestimate of the co-occurrence between ADHD and depression, an artifactual effect due to maternal rating bias.

In addition to being associated with rater bias, cross-rater discrepancies may reflect actual differences in children's behavior across settings, as well as different informant perspectives (Achenbach, 2011; De Los Reyes & Kazdin, 2005). Home and school settings vary in their activity demands, extent, and purpose, thus specific child behaviors may be more apparent in one context but not the other. Additionally, parents and teachers interact with the children in different contexts and have different frames of reference. Relative to mothers, teachers have the benefit of rating children against same-age peers, but have limited interaction with any given student and there is less variation in the teachers' interactions with a child. Behavior genetic studies provide support for the notion that mothers and teachers have different perspectives on children's ADHD symptoms while also revealing that mother and teacher ratings reflect a common underlying phenotype (Derks, Hudziak, Beijsterveldt, Dolan, & Boomsma, 2006; Martin, Scourfield, & McGuffin, 2002). Consequently, the association between ADHD and depression may differ across raters of ADHD, as mother and teacher reports appear to capture somewhat different facets of ADHD. Thus, a pattern of association consistent across raters of ADHD would strengthen the confidence that the co-occurrence between ADHD and depression is a true psychological phenomenon, independent of contextual variation and rater perspective.

The majority of the studies to date have relied on single sources of information, be it child or parent (typically mother), and to our knowledge no longitudinal population-based research that examined the link between ADHD and adolescent depression has accounted for potential rater bias. Prospective research, using multiple raters in a population-based sample is needed to elucidate these issues.

Gender differences in the relationship between ADHD and depression are not well understood. Given the disparity between sexes in the prevalence of depression and disruptive behavior disorders, as well as the earlier age of onset for disruptive disorders compared to

depression, most prospective studies of ADHD have relied on clinically-referred samples, in which girls are absent or represented in insufficient numbers to permit investigation of gender differences (e.g., Biederman, Petty, et al., 2008; Mannuzza et al., 1998). Several investigations have examined these issues prospectively in girls with ADHD, but boys were omitted from these studies, which precluded direct evaluation of gender effects (Biederman, Ball, et al., 2008; Hinshaw et al., 2006). Studies with mixed gender samples have yielded mixed findings. A prospective investigation found that clinically referred young boys and girls with ADHD had similarly elevated rates of depressive symptoms by mid-adolescence (Lahey et al., 2007). Interestingly, research utilizing the same sample found that by late-adolescence, girls with ADHD were at greater risk for adolescent depression and suicide attempts than boys with ADHD (Chronis-Tuscano et al., 2010). The implications of these findings however are constrained by the size of the female sample consisting only of 18 girls. In contrast, a prospective investigation in a diverse community sample found that gender did not moderate the association between childhood ADHD and elevated rates of adolescent internalizing disorders at 8-year follow-up (Bussing, Mason, Bell, Porter, & Garvan, 2010). Additional research is needed to reconcile these mixed findings and determine whether childhood ADHD predicts later depression to the same extent in boys as in girls.

While the comorbidity between ADHD and depression has been documented by a growing body of literature, the mechanisms underlying the overlap between the two disorders have been underexplored and remain poorly understood. Given the temporal precedence of ADHD to the onset of depression, the elucidation of etiological pathways linking ADHD and depression can have ample implications in applied settings, as risk factors that precede the onset of depression can be targeted early by prevention interventions. Research examining the etiological structure underlying the covariation between ADHD and depression, including the

bivariate analysis study included in this project, revealed that the overlap between the two disorders is governed by shared genetic factors operating either directly or indirectly via gene-environment correlations or interactions (J. Cole et al., 2009). It is thus plausible that ADHD increases exposure to environmental hazards which in turn predispose to later depression. A vast body of literature attests to an array of deficits and negative outcomes associated with ADHD, including antagonistic relationships with parents, poor academic performance, and social skills deficits, yet few studies have examined these factors as they relate to depression in youth with ADHD.

Negative transactions at home may contribute to the elevated risk of adolescent depression associated with ADHD. Children with ADHD experience higher levels of conflict with their parents than non-affected children (reviewed by Johnston & Mash, 2001) and longitudinal research has shown that conflict with parents is associated with later depressive symptomatology (Lewis, Collishaw, Thapar, & Harold, 2013; McLeod, Weisz, & Wood, 2007; Rueter, Scaramella, Wallace, & Conger, 1999). Disapproval and criticism by parents are experienced as aversive by the child, and may undermine self-esteem, reduce perceived mastery and self-efficacy and prompt development of negative self-schemas.

The antagonistic relationship between children with ADHD and their parents arises in part from transactional interactions with the child's characteristics. Parents of children with ADHD report elevated child-rearing stress and longitudinal evidence suggests that the fraught interactions between ADHD youth and their parents are related to the parents' feelings of powerlessness due to the perception that children are unresponsive to correction, which elicits and maintains ineffective parenting behaviors (Glatz, Stattin, & Kerr, 2011). Parents of children with ADHD engage in more attempts to control their children's behavior, use more power assertive discipline, are more demanding, less consistent, and use fewer positive parenting strategies

(Buhrmester, Camparo, Christensen, Gonzalez, & et al, 1992; Johnston & Mash, 2001; Johnston, 1996). Furthermore, over time, parents of children with ADHD increase their reliance on negative parenting practices (Glatz et al., 2011), which presumably leads to more discord with their children.

Parent characteristics also impact the interactions between children with ADHD and their parents. Maternal depression is a particularly relevant consideration when examining the effect of parent-child conflict on youth depression. Mothers of children with ADHD have elevated rates of depression (Chronis et al., 2003; Nigg & Hinshaw, 1998), and depressed mothers tend to have lower tolerance for their children's behaviors, to be more punitive, and engage in more conflictual behavior (Goodman & Gotlib, 1999). Consequently, among children with ADHD, a link between parent-child conflict and adolescent depression may only reflect transmission of risk for depression from mother to offspring. Thus, it is important, particularly from an intervention standpoint, to examine whether a potential effect of parent-child conflict on adolescent depression is contingent on maternal depression (i.e., extends to families with non-depressed mothers).

Few studies have examined family environment variables in the etiology of depression in youth with ADHD, and have yielded mixed findings. Ostrander & Herman (2006) showed that parent behavior management partially mediated the relationship between ADHD and depression in a sample of community children; (Drabick et al., 2006) reported that a family milieu characterized by conflict and low cohesion predicted depression in ADHD boys. In contrast, Biederman et al. (2008) did not find that family conflict was associated with depression in a prospective study of referred girls with ADHD. To date, we are not aware of any published study that focused on the impact of parent-child conflict on the risk for depression in youth with ADHD. Clearly more research is needed to elucidate the role of family environment, and in particular of parent-child conflict, in the etiology of depression among children with ADHD.

Another potential pathway through which ADHD could render children vulnerable to depression is via demoralization due to academic underperformance. A vast literature documents poorer scholastic outcomes in ADHD youth than in their non-affected counterparts (reviewed by Loe & Feldman, 2007). Children and adolescents with ADHD are more likely to have lower ratings on school subjects, achieve lower scores on standardized tests, are more likely to fail a grade and need more years to graduate from high school. The pattern of school difficulties starts early (e.g., preschool ADHD children are behind in school-readiness skills) and persists through adolescence and into the college years (Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993). Notably, population-based longitudinal evidence shows that ADHD is a strong and consistent predictor of later negative academic outcomes independent of conduct disorder symptoms and low socio-economic status (Galéra, Melchior, Chastang, Bouvard, & Fombonne, 2009). Given that scholastic difficulties associated with ADHD manifest early in development and follow a chronic course, a relevant question is whether they constitute a risk factor for depression. Competency-based models of depression posit that self-appraisals of academic and social incompetence heavily influence children's perception of themselves and contribute to the emergence of depressive symptoms (D. A. Cole, Jacquez, & Maschman, 2001).

Few longitudinal studies have examined whether academic deficits underlie the association between ADHD and later depression, and failed to find an effect (Biederman, Mick, & Faraone, 1998; Drabick et al., 2006; Meinzer et al., 2013). However, the issue warrants further investigation as previous studies had some limitations. Some of the reports relied on clinical male samples which constrains the generalizability of the findings (Biederman et al., 1998; Drabick et al., 2006). Meinzer et al. (2013) utilized a non-referred sample, but the participants were already in their late teenage years at baseline (mean age at baseline approximately 17 years) thus the findings may not generalize to children with ADHD. Age is a relevant consideration given that

children show a decrease in the value they attach to scholastic competence from 1st to 12th grade (Jacobs, Lanza, Osgood, Eccles, & Wigfield, 2002). Longitudinal research using non-referred samples and including a sufficient number of affected girls is required to resolve the issue of whether academic incompetence undermines the mood of children with ADHD leading to later depression.

Social adjustment in ADHD has received less attention in the ADHD scientific literature than academic deficits and behavioral problems, but it may play a key role in childhood and adolescence in defining self-perceptions of competence and influencing mood (Masten & Curtis, 2000), particularly as the importance of affiliation, peer acceptance and friendship increases in adolescence (Berndt, 1996). Theoretical and empirical literature supports cross-sectional and longitudinal links between social competence and depression from childhood to adolescence (K. B. Burt, Obradović, Long, & Masten, 2008; Hymel, Rubin, Rowden, & LeMare, 1990; Lee, Hankin, & Mermelstein, 2010; Nangle, Erdley, Newman, Mason, & Carpenter, 2003). Feedback from others on performance in key domains of functioning, including social functioning, had been posited to affect self-image and contribute to the development of subsequent depressive symptoms (D. A. Cole, 1990). Alternatively, poor social competence might serve as a diathesis in the development of depression, as individuals with social skills deficits encounter more stressors and also have fewer social resources to rely upon for support and assistance (Segrin, 2000).

The social difficulties experienced by youth with ADHD are broad and include difficulties both in dyadic friendships and in interactions within social groups. Children with ADHD have fewer friends than unaffected children and when they do establish friendships, the relationships are less stable and of lower quality (Mikami, 2010). Among children with ADHD, more than half may be rejected by their peers (Hoza et al., 2005) and there is evidence to suggest that children with ADHD face more social exclusion than children with internalizing or

externalizing alone, without ADHD (Asarnow, 1988; Gresham, MacMillan, Bocian, Ward, & Forness, 1998). Impaired social functioning observed in children with ADHD is established early in the development (Hoza et al., 2005) and persists through adolescence and into adulthood (Antshel et al., 2008; Shaw-Zirt, 2005). Notably, the persistent pattern of social difficulties associated with ADHD is not explained by comorbid conduct problems (Becker, Luebbe, & Langberg, 2012; Hoza et al., 2005; Ostrander & Herman, 2006).

Multifactorial contributions underlie the social competence deficits and challenges encountered by youth with ADHD. Inattention interferes with attending to social cues necessary for effective interaction and also limits opportunities for development of social skills through observational learning. Also, children with ADHD have difficulties integrating social information and tend to make social interpretations based on the most recently available social information (Milch-Reich, Campbell, Pelham Jr, Connelly, & Geva, 1999). Moreover, their behaviors (e.g., active, off-task, talkative, noisy, aggressive, rule-breaking, intrusive) render them aversive to peers, leading to social exclusion or neglect. Social rejection limits opportunities for practicing and acquiring adaptive social skills, which maintains social competence deficits.

Recent evidence indicates that youth with ADHD experience markedly elevated rates of victimization by peers, as indicated by both parent- and self-report (Sciberras, Ohan, & Anderson, 2011; Taylor, Saylor, Twyman, & Macias, 2010; Wiener & Mak, 2009). Population-based studies found that among school age children with ADHD the odds of being bullied are 7 to 10 times greater than those of non-affected children (Fisher et al., 2012; Holmberg & Hjern, 2008). Peer victimization appears to be more common among girls than boys with ADHD (Elkins, Malone, Keyes, Iacono, & McGue, 2011; Wiener & Mak, 2009), which is in line with evidence that peers are less tolerant of ADHD-related behaviors displayed by girls than by boys, perhaps due to violation of gender expectations (Diamantopoulou, Henricsson, & Rydell, 2005).

Bullying has been associated with a wide array of adjustment issues and mental health problems, including depression, social isolation, suicidal ideation and self-harm (Arseneault, Bowes, & Shakoor, 2009; Fisher et al., 2012; Hawker & Boulton, 2000). Notably, a population-based investigation reported that among females, but not males, victimization in childhood was associated with suicide attempts by early adulthood even when controlling for early symptoms of depression and conduct disorder (Klomek et al., 2009). Furthermore, a study of twins discordant for bullying demonstrated that victimization by peers is an environmentally mediated contributor to internalizing in children, over and above genetic vulnerability to being bullied and to develop internalizing issues (Arseneault et al., 2008). Overall, the evidence suggests that it is plausible that being the victim of bullying contributes to the development of depressive symptomatology in children with ADHD, although the hypothesis has yet to be put to empirical test. Prospective research is needed to examine the risk of depression associated with victimization among children with ADHD and to determine whether the deleterious effects of bullying are more pronounced among girls than boys.

The present study sought to address the limitations of previous literature. The study is well suited to test the robustness of the association between childhood ADHD and adolescent depression, as well as to investigate underlying mechanisms, and it has a number of advantages which strengthen inferences that could be drawn about the effects of ADHD on adolescent depression. First, the study has a prospective longitudinal design, following a population-based sample of 998 children from 11 years of age to 17 years of age, which made possible establishing temporal precedence by testing the association between ADHD symptoms exhibited up to age 11years and depression developed between the ages 11 and 17 years (a crucial developmental period in the emergence of depressive symptoms). Second, the study's recruitment strategy ensured elevated rates of ADHD and conduct disorder and an overrepresentation of affected girls,

which rendered it uniquely suited to examine gender differences in the effect of ADHD on subsequent depression, and to test the influence of conduct disorder on the relationship between ADHD and depression. Third, the study featured assessment procedures using different informants, which permitted evaluating the association between the ADHD and depression while minimizing potential rater bias associated with maternal reporting of child symptoms. Fourth, the study has rich data on academic, family and social functioning which allowed the investigation of potential pathways linking ADHD and adolescent depression.

The current study aimed at addressing the following questions:

1. Is childhood ADHD a predictor of adolescent depression and does the predictive association persist when attending to issues of rater bias effects? Is the risk of adolescent depression associated with ADHD comparable in boys and girls?
2. Does ADHD predict depression when taking into account the comorbidity with conduct disorder?
3. Does childhood ADHD predict suicidal ideation and suicide attempts through adolescence?
4. Does conflict between parent and child mediate the association between childhood ADHD and adolescent depression?
5. Does poor academic performance mediate the association between childhood ADHD and adolescent depression?
6. Does victimization by peers in childhood contribute to adolescent depression among children with ADHD?

1.2 METHOD

1.2.1 Participants

Participants were the 11-year-old twins participating in the Enrichment Study (ES), an extension of the Minnesota Twin and Family Study (MTFS), designed to yield a genetically-informative sample at risk for the development of substance abuse and augmented with children likely to be diagnosed with ADHD and conduct disorder. The sample consisted of 520 females and 478 males and was ascertained from Minnesota birth records of 2717 like-sex twin pairs born between 1988 and 1994. Of these, 82% were successfully located and their families were contacted to participate in the study in the year the twins became 11 years old. Seventy-six percent of the families were randomly assigned to be screened by phone for parent-reported symptoms of ADHD, conduct disorder and related behaviors. The screened families were invited to participate if at least one member of the twin pair met or exceeded a symptom threshold from a list of DSM symptoms of ADHD, conduct disorder, as well as indications of academic disengagement. The symptom threshold was determined using data from the 11-year old cohort from the MTFS and was calculated to enhance the probability of selecting twins having a diagnosis of ADHD or conduct disorder. The rest of the located families were recruited to the study without prior screening. Additional eligibility requirements for participating families included living within driving distance from the University of Minnesota Twin Cities campus and neither twin having an intellectual or physical impairment that interfered with their ability to complete the intake visit. Seventy-six percent of the eligible families completed the intake assessments, and of these, 48% were from the screened sample. The ES sample is being followed every three years, with the first and second follow-ups concluded. Ninety-one percent of the sample was Caucasian, representative of the children born in Minnesota in the birth years sampled (see Keyes et al. (2009) for more details on sample recruitment strategy and sample characteristics). In the present

study, data from intake, and the first and second follow-up assessments was used. At intake, mean age was 11.9 for both boys (SD= 0.41) and girls (SD= 0.44). At first follow-up, mean age was 15.0 for boys (SD = 0.51) and 15.1 for girls (SD = 0.59). At second follow-up, mean age was 17.8 for boys (SD = 0.41) and 17.9 for girls (SD = 0.50).

Of the 998 individual twins in the base sample, 938 twins (94.0%) had depression data at age-14 follow-up and 889 (89.1%) had depression data at age-17 follow-up. To determine whether loss at follow-up resulted in a biased sample, analyses were conducted to determine whether sex or diagnoses of ADHD, conduct disorder or depression affected the likelihood of participation at follow-up assessments, using generalized estimating equations for logistic regression to account for the relatedness of the participants. Attrition analyses indicated that boys and girls did not differ significantly in rate of participation at first ($\chi^2(1) = 0.19, p = 0.664$) or second ($\chi^2(1) = 0.23, p = 0.634$) follow-up. Among boys, a diagnosis of ADHD at intake did not significantly influence the likelihood of participation at the first ($\chi^2(1) = 0.01, p = 0.904$) or second ($\chi^2(1) = 0.07, p = 0.786$) follow-up. Also, a diagnosis of conduct disorder at intake did not significantly influence the likelihood of participation at the first ($\chi^2(1) = 0.52, p = 0.470$) or second ($\chi^2(1) = 0.75, p = 0.388$) follow-up. Similarly, a diagnosis of major depressive disorder at intake did not significantly influence the likelihood of participation at the first ($\chi^2(1) = 0.53, p = 0.465$) or second ($\chi^2(1) = 1.31, p = 0.253$) follow-up. Among girls, a diagnosis of ADHD at intake did not significantly influence the likelihood of participation at the first ($\chi^2(1) = 1.29, p = 0.255$) or second ($\chi^2(1) = 0.28, p = 0.597$) follow-up. Also, a diagnosis of conduct disorder at intake did not significantly influence the likelihood of participation at the first ($\chi^2(1) = 0.761, p = 0.383$) or second ($\chi^2(1) = 1.02, p = 0.313$) follow-up. Similarly, a diagnosis of major depressive disorder at intake did not significantly

influence the likelihood of participation at the first ($\chi^2(1) = 0.19, p = 0.659$) or second ($\chi^2(1) = 0.24, p = 0.621$) follow-up.

1.2.2 Measures

After being provided a description of the study, participants gave written consent or assent, as appropriate. At every assessment, each parent and each member of the twin pair was interviewed separately by a different interviewer who held a B. A. or M. A. in psychology and underwent extensive training. Symptoms at intake were assessed lifetime, whereas symptoms at follow-ups were assessed since the last assessment. At intake and first follow-up, maternal and self-reports of each twin's symptoms of ADHD, conduct disorder and major depressive disorder were obtained using a modified version of the Diagnostic Interview for Children and Adolescents – Revised (DICA-R) (Reich, 2000; Welner, 1987). At second follow-up, twins underwent assessment for depression using the Structured Clinical Interview for DSM-IV; mothers reported on the twins' symptoms of depression using the parent version of the DICA-R. Symptoms were counted toward a diagnosis if endorsed by either child or mother, using a best-estimate procedure, which provides better validity than using either rater alone (S. A. Burt, Krueger, McGue, & Iacono, 2001). Diagnoses were made at two levels of certainty: definite and probable. At the definite level, a diagnosis was assigned if all the necessary criteria were met; at the probable level, all necessary symptom criteria were present with the exception of one symptom. This assessment method was used to minimize the likelihood of false negative diagnoses and prevent underreporting in community sample and when assessing lifetime psychopathology (Iacono, Carlson, Taylor, Elkins, & McGue, 1999). The diagnoses obtained have good reliability with kappas exceeding .74. At intake, 25.6% of the sample was diagnosed with ADHD (144 boys and 111 girls), and

12.4% was diagnosed with conduct disorder (90 boys and 34 girls), indicating that the study's strategy of recruiting at-risk children was successful.

Up to three teachers per twin provided ratings of ADHD symptoms and the mean of the teacher ratings at intake was utilized for the twin's teacher rating of ADHD variable. Suicide attempts were assessed lifetime at age-17 follow-up, part of a Life Events interview. Whether a twin ever attempted suicide was used for the twin's categorical suicide attempt variable. The lifetime suicidal ideation variable was derived from the suicidality item on the major depressive disorder clinical interview. The participants were administered the item pertaining to suicidality only if they endorsed at least two weeks of depressed mood or anhedonia.

Parent- Child Conflict

Characteristics of the parent-child relationship were assessed using the Parental Environment Questionnaire (PEQ) at intake. The PEQ is a 42-item survey developed by MTFS researchers to provide multi-informant perceptions of the parent-child relationship and has been shown to reliably assess parent-child relationships. A detailed description of the PEQ, its development, rationale and psychometric properties can be found elsewhere (Elkins, McGue, & Iacono, 1997). In this study, we utilized the Conflict scale (internal consistency reliability $\alpha = 0.82$; McGue et al., 2005), which measures the extent to which the relationship between parent and child is characterized by anger, tension and disagreement (e.g., "My parent often criticizes me" and "My parent and I often get into arguments"). The Conflict scale consists of 12 items rated on a 4-point scale (1 = definitely true; 2 = somewhat true; 3 = somewhat false; 4 = definitely false) and scored such that high scores corresponded to high levels of parent-child conflict. The children provided two sets of ratings, describing their relationship with their mother and their father, respectively. Mothers also provided their own experience of the relationship with the child. The item content

was essentially the same across informants, with minor word changes appropriate for particular raters. To create a composite index of conflict with parents, the ratings of the twins and their mothers were averaged. The children's ratings of their relationship to their mother and their father were highly correlated (r = 0.86), consistent with research based on self-report utilizing the PEQ (McGue et al., 2005) or other measures (Juang & Silbereisen, 1999). Therefore, child's ratings of mother-child and father-child relationships were first averaged to obtain a composite measure of the child's perceptions of his relationships with his parents. The PEQ questionnaires were mailed to families prior to their assessment visit. If the PEQ was not brought to the in-person visit or a completed PEQ was not obtained by the end of the visit, participants were asked to complete it at home and return it by mail. An additional telephone prompt was made if the PEQ was still not received. At intake, 96% of the twins had child PEQ reports and 94% had mother PEQ reports.

Academic Performance

Academic performance at intake was assessed using the grade point average (GPA), calculated as the mean of grades in language arts, math, social studies, and science, provided by up to three teachers, on a standard 0.0 (Fs) to 4.0 (As) scale. As shown in a different sample (Johnson, McGue, & Iacono, 2006), the mean grades provided by the teachers on these core subjects correlated highly (r = 0.89) with overall GPA from school transcripts. Teacher ratings of academic performance were available for 81% of the sample.

Victimization by peers

Victimization by peers was assessed by asking each child at intake "Have you ever been bullied or picked on a lot by other kids?", part of a Live Events interview.

1.2.3 Statistical Analyses

The association between ADHD and depression and suicidal behavior outcomes was investigated utilizing logistic regression analyses. A series of increasingly complex logistic models were fitted to predict the categorical variables of depression diagnosis, suicide attempt and suicidal ideation at age 17. Given the recruitment strategy utilized by the ES study, aimed at oversampling pairs of twins with disruptive disorders, the participants had different probabilities of selection into the study, depending on whether they were selected from the unscreened sample or the screened sample. This rendered untenable the assumption that individual observations have equal probability of selection into the sample, an assumption which is inherent in analytic procedures in most statistical software packages. Sampling weights can be used to mathematically address the issue of unequal selection probabilities, by assigning the twin pairs from the unscreened sample greater weights and the twin pairs from the screened sample lower weights. The assigning of weights was based on the assumption that the unscreened sample was representative of the population sampled. The procedure CSLOGISTIC from the Complex Samples module included in the statistical package SPSS 21 was used to fit logistic models. Complex Samples module provides statistical tools suitable for analysis of samples that differ from the simple random samples due to unequal selection probabilities. The sample weights were added to the analytic procedure CSLOGISTIC. The generalized estimating equations (GEE) method was used in CSLOGISTIC, to account for the clustering of observations given that the participants were twins. Participants with missing values on any variables used in individual statistical procedures were excluded from the analyses.

Mediation Analyses

The mediation analyses were conducted using the product of coefficients approach as described by MacKinnon et al. (2002). For each individual mediator, three regression equations corresponding to the path diagrams in Figure 1.1 were used to investigate mediation:

$$Y = i_1 + cX + e_1 \quad (1)$$

$$Y = i_2 + c'X + bM + e_2 \quad (2)$$

$$M = i_3 + aX + e_3 \quad (3)$$

where i_1, i_2, *and* i_3 represent the intercepts and e_1, e_2, *and* e_3 represent the unexplained or error variability. The paths in Figure 1.1 can be quantified by unstandardized regression coefficients. Equation 1 established the total effect of the independent variable X (childhood ADHD symptom count) on the dependent variable Y (age 17 diagnosis of depression), without taking into consideration mediator variables. The total effect was denoted by *c*. Equation 2 established the direct effect *c'* of the independent variable childhood symptoms of ADHD on the dependent variable, adolescent depression, adjusted for the contribution of the hypothesized mediator M. Equation 2 also established the relation between the mediator M and depression taking into account the effect of ADHD symptoms, estimated by the regression coefficient *b*. The parameter *a* in Equation 3 related the independent variable, ADHD symptoms, to the mediator M. As shown in Figure 1.1, the independent variable can influence the dependent variable directly, or indirectly, through the mediator M. The mediated effect, also referred to as the indirect effect, by which the independent variable influences the dependent variable through M may be calculated as either $\hat{c} - \hat{c}'$ or $\hat{a}\hat{b}$, where ^ indicates regression estimates. The value of the mediated effect $\hat{c} - \hat{c}'$ corresponds thus to the reduction in the effect of the independent variable on the dependent variable when adjusted for the contribution of the mediator. The alternative way of computing the mediated effect, $\hat{a}\hat{b}$, reflects how much a 1 unit change in the independent variable affects the dependent variable indirectly through the mediator.

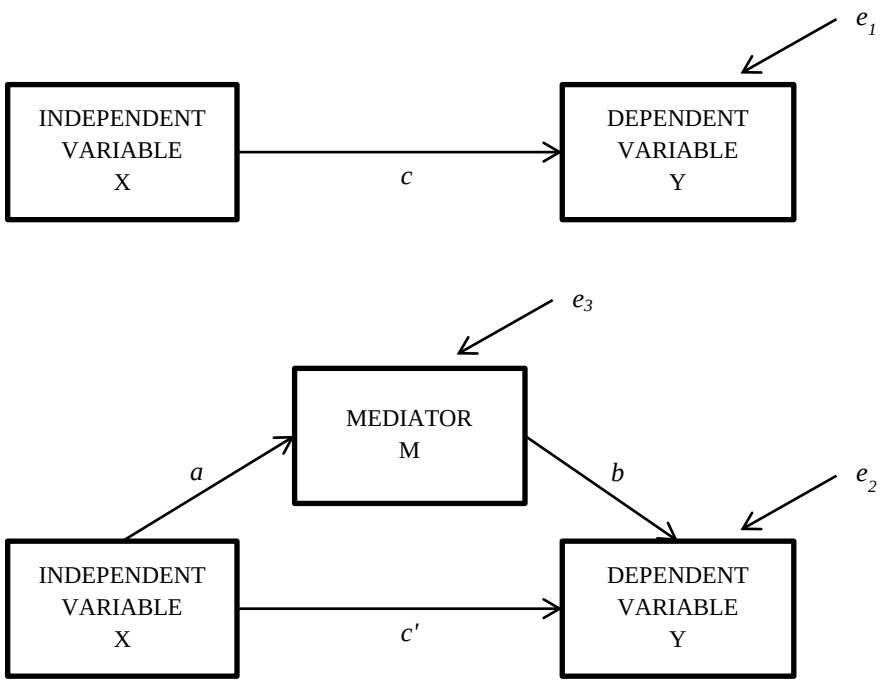

Figure 1.1 Path diagram for the single mediation model.

The criteria for establishing mediation used in the current study were as follows:

1. The independent variable is significantly related to the dependent variable, as indicated by the coefficient $\hat{c}$ in equation 1.
2. The independent variable is significantly related to the hypothesized mediation M, as indicated by the coefficient $\hat{a}$ in equation 3.
3. The mediating variable is significantly related to the dependent variable when the independent variable X is controlled, as evaluated by the coefficient $\hat{b}$ in equation 2; or, there is a significant interaction indicating that the relationship between the mediator and the dependent variable differs across levels of the mediator (Kraemer, Kiernan, Essex, & Kupfer, 2008).

The first step in establishing mediation is controversial because even in the absence of a significant relation between the independent variable and the dependent variable, mediation can occur, when the mediated effect and the direct effect have opposite signs, as in suppression models (MacKinnon, 2007).

When the parameters in Equations 1 through 3 are estimated using ordinary least squares regression or maximum likelihood estimation for continuous measures, the mediated effect equals the difference between the total effect and the direct effect (Baron & Kenny, 1986).

$$\widehat{\boldsymbol{ab}} = \hat{\boldsymbol{c}} - \hat{\boldsymbol{c}}'$$

However, when the dependent variable is categorical, as in the current study, requiring logistic (or probit) regression to estimate the mediation paths, the mediated effect $\hat{a}\hat{b}$ does not equal the difference between the total effect $\hat{c}$ and the direct effect $\hat{c}'$ because the unstandardized regression coefficients across equations are not on the same scale. Therefore, before computing the mediated effect, the logistic regression coefficients were standardized as described by MacKinnon & Dwyer (1993). The logistic regression estimate $\hat{c}$ was divided by the standard deviation of the criterion Y in Equation 1, computed as follows:

$$\widehat{\boldsymbol{\sigma}}_{\boldsymbol{Y}} = \sqrt{\hat{\boldsymbol{c}}^{\boldsymbol{2}}\widehat{\boldsymbol{\sigma}}_{\boldsymbol{X}}^{\boldsymbol{2}} + \frac{\boldsymbol{\pi}^{\boldsymbol{2}}}{\boldsymbol{3}}}$$

where $\widehat{\boldsymbol{\sigma}}_{\boldsymbol{X}}^{\boldsymbol{2}}$ denotes the variance estimate of the independent variable X. The logistic regression estimates $\hat{b}$ and $\hat{c}'$ were divided by the standard deviation of the criterion Y in equation 2.

$$\widehat{\boldsymbol{\sigma}}_{\boldsymbol{Y}} = \sqrt{\hat{\boldsymbol{c}}'^{\boldsymbol{2}}\widehat{\boldsymbol{\sigma}}_{\boldsymbol{X}}^{\boldsymbol{2}} + \widehat{\boldsymbol{b}}^{\boldsymbol{2}}\widehat{\boldsymbol{\sigma}}_{\boldsymbol{M}}^{\boldsymbol{2}} + \boldsymbol{2}\hat{\boldsymbol{c}}'\widehat{\boldsymbol{b}}\widehat{\boldsymbol{\sigma}}_{\boldsymbol{XM}} + \frac{\boldsymbol{\pi}^{\boldsymbol{2}}}{\boldsymbol{3}}}$$

where $\widehat{\boldsymbol{\sigma}}_{\boldsymbol{X}}^{\boldsymbol{2}}$ denotes the variance estimate of the independent variable X, $\widehat{\boldsymbol{\sigma}}_{\boldsymbol{M}}^{\boldsymbol{2}}$ denotes the variance estimate of the mediator M, and $\widehat{\boldsymbol{\sigma}}_{\boldsymbol{XM}}$ the covariance of X and M. The estimates of the standard errors of the logistic regression coefficients were scaled in the same fashion as the coefficients.

The standardized estimates were then used in the calculation of the mediated effect $\hat{a}\hat{b}$ and its standard error. The 95% confidence intervals for the mediated effect were computed using the formula $\boldsymbol{\hat{a}\hat{b} \pm 1.96 \cdot s_{\hat{a}\hat{b}}}$. Using standardized estimates, the standard error of the mediated effect was computed based on the formula derived by (Sobel, 1982):

$$\boldsymbol{s_{\hat{a}\hat{b}} = \sqrt{\hat{a}^2 s_{\hat{b}}^2 + \hat{b}^2 s_{\hat{a}}^2}}$$

where $\boldsymbol{s_{\hat{a}}^2}$ and $\boldsymbol{s_{\hat{b}}^2}$ corresponded to the squared standard errors of $\boldsymbol{\hat{a}}$ and $\boldsymbol{\hat{b}}$. Also using standardized estimates, the proportion of the total effect explained by the mediator M was computed as:

$$\frac{\hat{c} - \hat{c'}}{\hat{c}}$$

An interaction term was not included in the initial mediation analyses, but for each hypothesized mediator, interaction terms were added in additional analyses to test for moderated mediation, more specifically to evaluate whether the effect of the mediator was contingent on gender. Note that it is not necessary for the mediated effect to be statistically significant in order to examine moderated mediation effects (Preacher, Rucker, & Hayes, 2007). The moderated mediation process is displayed in conceptual and statistical form in Figure 1.2, panel A and B, respectively. As shown in Figure 1.2, the mediated effect varies at different levels of the moderator. More specifically in this case, the mediated effect of childhood ADHD on adolescent depression, via the mediator M, differs for males and females.

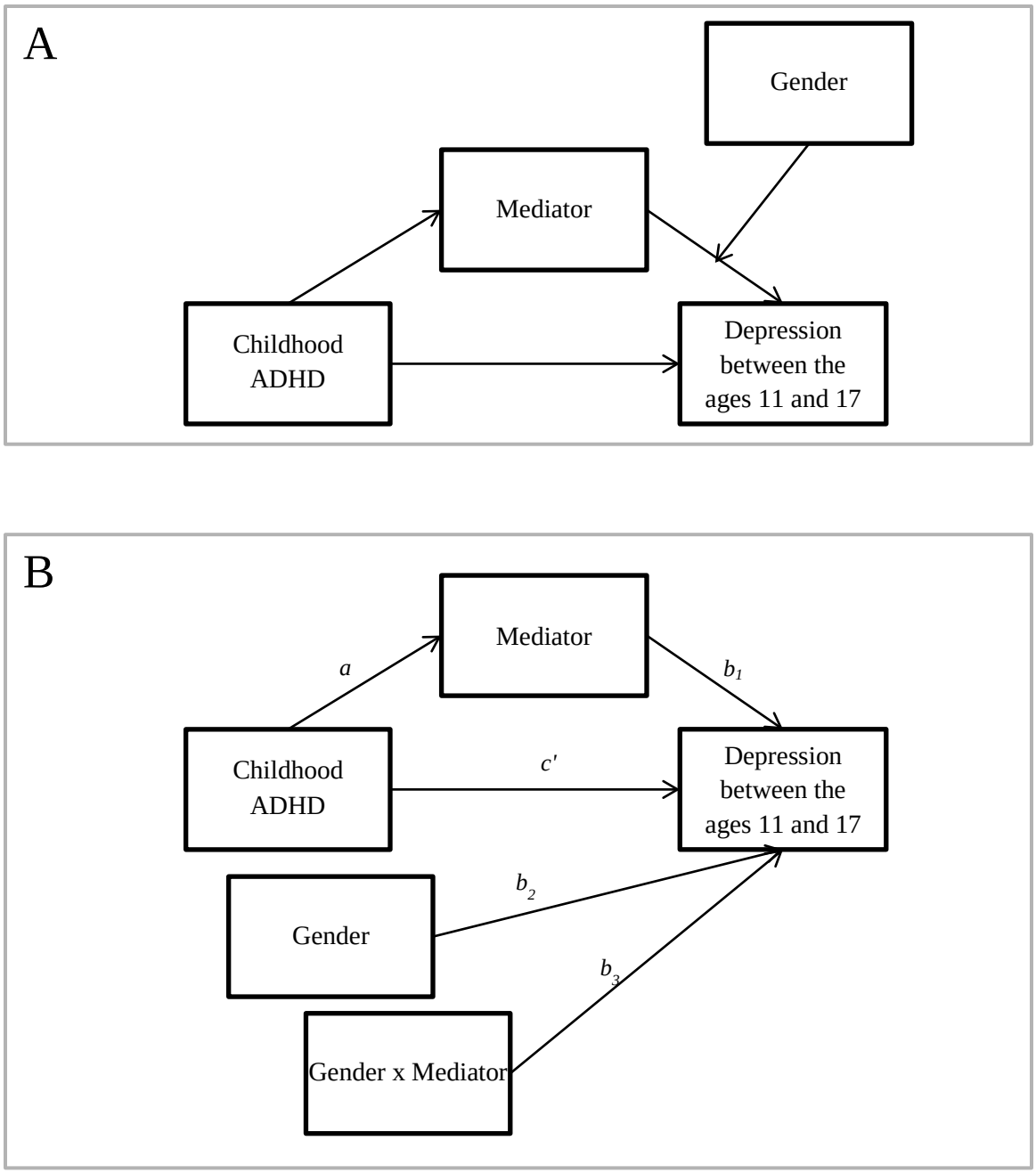

Figure 1.2 Moderated mediation model presented in conceptual (panel A) and statistical (panel B) form.

1.3 RESULTS

Table 1.1 summarizes the prevalence of ADHD, conduct disorder and depression at intake (age 11) and of depression by age-17 follow-up. Diagnoses at intake were lifetime; depression diagnoses at age-17 follow-up were based on symptoms that occurred in the interval between intake and age-17 follow-up. Lifetime prevalence of depression at age 11 was similar for boys and girls, ($\chi^2(1) = 0.17, p = 0.685$), consistent with expectations at this young age (Merikangas & Avenevoli, 2002). In the interval between intake and age-17 follow-up, more girls met the diagnostic criteria for depression than boys ($\chi^2(1) = 8.39, p = 0.004$), consistent with research showing greater rates of depression in adolescence among females than among males (Merikangas et al., 2010). With regard to ADHD, girls had fewer symptoms than boys (for girls, M = 3.17, SD = 4.06; for boys, M = 4.54, SD = 4.51; $t(996) = 5.04$, $p < 0.001$). However, among the 255 children with a diagnosis of ADHD, there were no statistically significant sex differences in the number of symptoms (for girls, M = 9.53, SD = 3.05; for boys, M = 10.13, SD = 2.95; $t(253) = 1.59$, $p = 0.114$), suggesting similar overall ADHD severity among affected boys and girls. Similarly, at intake, girls had fewer symptoms of conduct disorder than boys (for girls, M = 0.46, SD = 0.82; for boys, M = 1.00, SD = 1.35; $t(996) = 7.69$, $p < 0.001$), but among the 124 children with a diagnosis of conduct disorder there were no significant sex differences in the number of symptoms (for girls, M = 2.76, SD = 0.96; for boys, M = 3.18, SD = 1.38; $t(122)$ = 1.61, $p < 0.111$).

At age-17 follow-up, 3.0% of participants endorsed ever attempting suicide, a lifetime prevalence rate slightly lower than that reported by prior epidemiological studies, in which rates ranging from 3.1% to 8.8% are typical (Nock et al., 2008). The lifetime prevalence of suicidal ideation was 14.1% which, due to the study's assessment procedure of suicidal ideation (described in Methods), was below the rates previously reported in adolescents (19.8%-24.0%).

As shown in Table 1.1, the subset of participants who attempted suicide or experienced suicidal ideation was predominantly female, consistent with epidemiological reports (Nock et al., 2008). Of the participants endorsing attempting suicide by age 17 years, the majority (85%) had also met criteria for depression at least once by that age. Of the suicide ideators, 92% had been diagnosed with depression by age 17 years.

For ease of presentation, hereinafter "childhood ADHD symptoms" refer to the number of symptoms of ADHD assessed lifetime at intake. "Adolescent depression" denotes that by the age-17 follow-up a participant met the diagnostic criteria for major depressive disorder at least once since intake.

Table 1.1 Prevalence of ADHD, Conduct Disorder and Depression at Intake and of Depression, Suicide Attempt and Suicidal Ideation at Age 17 Follow-up, by Sex [a]

		Males		Females		Total	
Age 11[b]							
N		478		520		998	
ADHD	N (%)	144	(30.1)	111	(21.3)	255	(25.6)
Conduct Disorder	N (%)	90	(18.8)	34	(6.5)	124	(12.4)
Major Depression	N (%)	28	(5.9)	27	(5.2)	55	(5.5)
Age 17							
N		432		469		901	
Major Depression [c]	N (%)	77	(17.8)	128	(27.3)	205	(22.8)
Suicide Attempt [d]	N (%)	5	(1.1)	22	(4.7)	27	(3.0)
Suicidal Ideation [d]	N (%)	45	(10.5)	81	(17.5)	126	(14.1)

[a] DSM-IV diagnoses, reported at both probable and definite levels of certainty.
[b] Lifetime diagnoses at intake.
[c] Diagnosis based on symptoms occurring since intake.
[d] Lifetime at age 17 follow-up

Do childhood symptoms of ADHD predict adolescent depression?

As indicated in Table 1.2 (Model 1), the logistic regression analysis revealed that childhood ADHD symptoms predicted adolescent depression, with one standard deviation increase in ADHD symptoms raising the odds for depression by 51% (OR = 1.51, 95% CI = 1.24 – 1.82, $p < 0.001$), after controlling for age, sex, and depression status at intake.

Is the association between childhood symptoms of ADHD symptoms and adolescent depression an artifact attributable to rater bias effects?

Two approaches were utilized to test whether potential rater bias effects due to maternal reporting of child psychopathology symptoms explained the association between childhood symptoms of ADHD and adolescent depression in the offspring. In the first approach, it was tested whether the effect of childhood symptoms of ADHD on adolescent depression was carried through via maternal depression. In the second approach, the relation between offspring ADHD and adolescent depression was re-examined utilizing teacher ratings of ADHD symptoms and thus eliminating the potential confounding effect of maternal reporting on child psychopathology. As shown in Table 1.2 (Model 2), when adjusting for effects of maternal depression, childhood ADHD symptoms predicted adolescent depression, with one standard deviation increase in ADHD symptoms raising the odds of depression by 44% (OR = 1.44, 95% CI = 1.17 – 1.76, p = 0.001). There were no significant interaction effects between maternal depression and child symptoms of ADHD in predicting adolescent depression (Wald F = 1.41, p = 0.236). This result confirms in a population sample recent prospective findings in a clinical sample showing that childhood ADHD predicts depression through adolescence even when accounting for maternal depression (Chronis-Tuscano et al., 2010).

The correlation between teacher ratings of ADHD and symptoms of ADHD was 0.48, a concordance rate comparable to that reported in other studies (Papageorgiou, Kalyva, Dafoulis, & Vostanis, 2008; Thapar, Harrington, Ross, & Mcguffin, 2000). A logistic regression using teacher ratings of ADHD at intake to predict adolescent depression showed that teacher-reported symptom dimension of ADHD was predictive of depression when controlling for age, sex and depression at intake. Specifically, an increase of one standard deviation in teacher ratings of ADHD increased the odds of adolescent depression by 28% (OR = 1.28, 95% CI = 1.02 – 1.61, p = 0.033). There were no significant interaction effects between teacher ratings of ADHD and sex in predicting later depression (Wald F = 3.25, p = 0.072).

Table 1.2 Risk of Depression by 17 Years of Age, ORs (95% CI)[a, b] .

	Model 1	Model 2
Predictor	OR (95% CI)	OR (95% CI)
Female Sex	**1.67** (1.05 – 2.66)	**1.78** (1.11 – 2.88)
ADHD Symptoms [c]	**1.51** (1.24 – 1.82)	**1.44** (1.17 – 1.76)
Maternal Depression [d]		**2.20** (1.37 – 3.53)

[a] Odds ratios (ORs) adjusted for depression at intake and age at follow-up.
ORs reflect the increase in the odds of developing depression associated with a 1 SD increase in the indicated symptom dimension, or with the presence of the indicated diagnosis.
Statistically significant ORs are shown in boldface type.
[b] ORs are associated with main effects. There were no statistically significant interactions.
[c] Lifetime symptom count at intake.
[d] Lifetime diagnosis.

Is the association between childhood ADHD and adolescent depression explained by conduct disorder?

Two sets of logistic regression analyses were conducted to investigate the influence of conduct disorder on the association between ADHD and later depression. The top section of Table 1.3 shows the results of analyses using symptoms of ADHD and symptoms of conduct disorder at intake to predict adolescent depression. In order to provide strong evaluation of the influence of

conduct disorder on the association between ADHD and later depression, given that the prevalence of conduct problems increases in adolescence (32% increase from ages 11 to 14 years in this sample), an additional set of analyses was conducted, utilizing the age-14 follow-up data. The bottom section of Table 1.3 shows the results of analyses using conduct disorder symptoms at age 14 and ADHD symptoms at intake to predict depressive episodes developed between the ages 14 and 17 years. To determine whether the influence of conduct problems on the risk for depression was more elevated at higher levels of ADHD symptoms, a conduct disorder symptoms × ADHD symptoms interaction term was added to the models. The interaction was not statistically significant when predicting depression between 11 and 17 years of age (Wald F = 0.21, $p = 0.650$), or depression between 14 and 17 years of age (Wald F = 2.29, $p = 0.131$), suggesting a similar relationship between ADHD and later depression across different degrees of conduct problems. All the analyses controlled for sex, depression status at intake and age at age-17 follow-up.

The results revealed that ADHD symptoms uniquely predicted adolescent depression, even after adjusting for conduct disorder symptoms at age 11 years, with an increase of one standard deviation in ADHD symptoms raising the odds of adolescent depression by 48% (OR = 1.48, 95% CI = 1.21 – 1.81, $p < 0.001$). Conduct disorder symptoms at intake did not predict adolescent depression (OR = 1.04, 95% CI = 0.84 – 1.30, $p = 0.693$) when controlling for ADHD symptoms. Similarly, ADHD symptoms at intake uniquely predicted the occurrence of at least one depressive episode between the ages 14 and 17 years, even when taking into account conduct disorder symptoms at age 14 (OR = 1.35, 95% CI = 1.09 – 1.68, $p = 0.006$). Comparison of the adjusted and fully adjusted ORs for conduct disorder symptoms, both at age 11 and at age 14, revealed that while conduct disorder symptoms predicted subsequent depression, their predictive value disappeared after adjustment for ADHD symptoms.

Is the risk of adolescent depression associated with childhood ADHD comparable in boys and girls?

In order to determine the presence of sex differences in the association between childhood ADHD symptoms and adolescent depression, an ADHD dimension × sex term was added to the logistic regression model. The interaction was not statistically significant (Wald F = 2.69, $p = 0.102$). Also, as indicated above, the interaction between teacher ratings of ADHD and sex in predicting adolescent depression was not statistically significant at 0.05 level (Wald F = 3.25, $p = 0.072$). As both interactions approached statistical significance, with the interaction term in the regression, odds ratios of adolescent depression associated with an increase of one standard deviation in ADHD dimension were computed separately for males and females. A comparison of the odds ratios for males and females suggested that symptoms of ADHD were associated with higher risk of adolescent depression in females than in males ($OR_{female} = 1.76$, 95% CI = 1.36 – 2.27; $OR_{male} = 1.28$, 95% CI = 0.96 – 1.70). Similar pattern of results was obtained when using teacher ratings of ADHD ($OR_{female} = 1.68$, 95% CI = 1.14 – 2.48; $OR_{male} = 1.09$, 95% CI = 0.83 – 1.43).

Table 1.3 Risk of Depression, ORs (95% CI)[a, b]

	ADHD Symptoms At Age 11 Years		CD Symptoms At Age 11 Years	
Depression Between 11 and 17 years of Age				
Adjusted	**1.51**	(1.24 – 1.82)	1.23	(0.99 – 1.53)
Fully Adjusted	**1.48**	(1.21 – 1.81)	1.04	(0.84 – 1.30)

	ADHD Symptoms At Age 11 Years		CD Symptoms At Age 14 Years	
Depression Between 14 and 17 years of Age				
Adjusted	**1.44**	(1.18 – 1.76)	**1.32**	(1.05 – 1.65)
Fully Adjusted	**1.35**	(1.09 – 1.68)	1.19	(0.92 – 1.54)

OR, odds ratio; CI, confidence interval; CD, conduct disorder
[a] ORs reflect the increase in the odds of developing depression associated with one standard deviation increase in the indicated symptom dimension. Statistically significant ORs are shown in boldface type.
[b] Adjusted ORs indicate adjustment for sex, depression at intake, and age at age 17 follow-up. Fully Adjusted ORs indicate additional control for ADHD symptoms or CD symptoms.

Does childhood ADHD predict lifetime suicidal ideation and suicide attempts through age 17 years?

Table 1.4 presents the results of logistic regression analyses using symptoms of ADHD and conduct disorder at intake to predict lifetime suicidal ideation and suicide attempts at age 17 years, while controlling for depression at intake, sex, and age. As shown in Table 1.4 (Model 1 and Model 3), ADHD symptoms were significant predictors of suicide attempts and suicidal ideation by age 17 years, with one standard deviation increase in ADHD symptoms raising the odds of suicide attempt by 81% (OR = 1.81, 95% CI = 1.23 – 2.65, $p = 0.002$) and of suicidal ideation by 50% (OR = 1.50, 95% CI = 1.24 – 1.82, $p < 0.001$). However, ADHD symptoms predicted suicide attempts only when their contribution was not adjusted for the effects of conduct disorder. Conduct disorder symptoms at intake significantly predicted suicide attempts

by age 17 years. Remarkably, even a single symptom of conduct disorder raised the odds of suicide attempt by 57% (OR = 1.57, 95% CI = 1.23 – 2.00, $p < 0.001$) while also controlling for symptoms of ADHD. Female sex was a strong predictor of suicide attempts and suicidal ideation, but there were no significant interactions between sex and ADHD symptoms or conduct disorder symptoms in any of the models summarized in Table 1.4, suggesting similar associations between predictors and suicide outcomes for males and females.

Table 1.4 Lifetime Risk of Suicide Attempt and Suicidal Ideation at Age 17 Years, ORs (95% CI)[a, b]

	Suicide Attempt				Suicidal Ideation			
	Model 1		Model 2		Model 3		Model 4	
Predictor	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Female Sex	**6.54**	(2.59 – 16.53)	**9.94**	(3.43 – 28.80)	**2.09**	(1.20 – 3.64)	**2.21**	(1.24 – 3.95)
ADHD Symptoms [c]	**1.81**	(1.23 – 2.65)	1.50	(0.98 – 2.29)	**1.50**	(1.24 – 1.82)	**1.42**	(1.14 – 1.77)
CD Symptoms [c]			**1.67**	(1.26 – 2.20)			1.16	(0.93 – 1.44)

OR, odds ratio; CI, confidence interval; CD, conduct disorder

[a] Odds ratios (ORs) adjusted for depression at intake and age at 17-year follow-up. Statistically significant ORs are shown in boldface type. ORs reflect the increase in the odds of outcomes associated with a 1 SD increase in the indicated symptom dimension.

[b] ORs are associated with main effects. There were no statistically significant interactions.

[c] Lifetime symptom count at intake.

1.3.1 Mediation Analyses

As recommended by MacKinnon (2007), to ensure consistency across mediation regression equations, each set of mediation analyses was conducted using only observations that had valid data on all the relevant variables (i.e., independent, dependent and mediating variable). Consequently, given the variation in sample size, the total effect (i.e., the effect of the predictor on the outcome without the mediator in the model) was estimated for each of the hypothesized mediators. All the mediation analyses controlled for sex, age and depression at baseline. Table 1.5 provides a comparison on the hypothesized mediators between children with and without ADHD. At intake, children with ADHD experienced higher conflict with parents, achieved significantly lower GPA scores and had greater rates of victimization by peers compared to unaffected children.

Table 1.5 Comparison of Stressors between Children with ADHD and Unaffected Children at Age 11 Years

Continuous Measures (rater)	Mean (SD)	$\chi^2(1)$	p	Cohen's d
Conflict with parents (CM)*		23.07	< 0.001	0.39
No ADHD (*n* = 683)	50.00 (10.00)			
ADHD (n = 220)	53.79 (9.06)			
Grade-point average (T)		44.61	< 0.001	0.60
No ADHD (*n* = 606)	3.00 (0.84)			
ADHD (n = 199)	2.50 (0.83)			
Categorical Measures (rater)	**Frequency (%)**	**$\chi^2(1)$**	**p**	**OR**
Ever bullied a lot (C)		36.14	< 0.001	2.81
No ADHD (*n* = 742)	150 (20.2%)			
ADHD (n = 255)	106 (41.6%)			

Rater: C = child, T = teacher, P = parent, M = mother
*Scores are presented as T scores relative to the No ADHD group in order to facilitate comparison on variables without a well-established scale.

Does conflict between parent and child mediate the association between childhood ADHD symptoms and adolescent depression?

Figure 1.3 displays the results of the mediation analyses evaluating whether antagonistic relationships with parents at age 11 years mediated the association between childhood ADHD symptoms and adolescent depression. Regression coefficients are also presented in Table 1.6. ADHD symptoms predicted adolescent depression ($c = 0.10$, $SE_c = 0.02$, $p < 0.001$). A 1-symptom increase in the number of childhood symptoms of ADHD was associated with an increase of 0.10 in the logit of adolescent depression. ADHD symptoms were significantly related to conflict with parents at age 11 ($a = 0.67$, $SE_a = 0.09$, $p < 0.001$). A 1-symptom increase in the number of childhood symptoms of ADHD was associated with an increase of 0.67 in the measure of parent-child conflict. Conflict with parents at age 11 years was predictive of adolescent depression ($b = 0.05$, $SE_b = 0.01$, $p < 0.001$) when controlling for ADHD symptoms. A 1-unit increase in the measure of parent-child conflict was associated with a 0.05 increase in the logit for depression when controlling for the effect of ADHD symptoms. ADHD symptoms remained a significant predictor of depression ($c' = 0.07$, $SE_{c'} = 0.03$, $p = 0.009$) when controlling for conflict with parents. The results indicated that the prospective association between childhood ADHD and adolescent depression was partially mediated by conflict with parents. To estimate the magnitude of the mediated effect, its confidence intervals, and the proportion of the total effect explained by the mediating variable, the logistic regression coefficients were standardized following the procedure described in the Method section ($b_{std} = 0.03$, $c_{std} = 0.05$, $c'_{std} = 0.03$). Plugging in the standardized coefficients into the usual $c - c'$ formula yields a mediated effect of 0.02 (95% CI = 0.01 – 0.03). To compute the proportion of the total effect that is mediated, the $(c - c')/c$ formula was utilized, with standardized coefficients. The result indicated that conflict with parents explained 34% of the effect of childhood ADHD on adolescent depression.

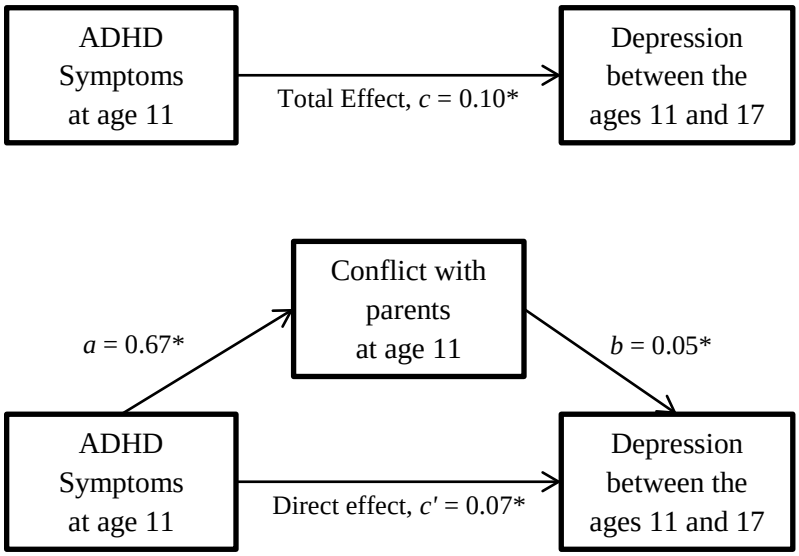

Figure 1.3 Mediation model for conflict with parents (* p < 0.01)

Table 1.6 Unstandardized Path Coefficients for Single Mediator Models Predicting Depression between Ages 11 and 17 Years from ADHD Symptoms at Age 11 Years

Hypothesized Mediator	Path	Regression Coefficient	p
Conflict with Parents			
	c	**0.10**	<0.001
	a	**0.67**	<0.001
	b	**0.05**	<0.001
	c'	**0.07**	0.009
Grade-Point Average			
	c	**0.10**	<0.001
	a	**-0.07**	<0.001
	b	-0.15	0.255
	c'	**0.09**	0.002
Being Bullied			
	c	**0.09**	<0.001
	a	**0.12**	<0.001
	b	0.29	0.230
	c'	**0.09**	<0.001

Path coefficients correspond to the mediation path diagram shown in Figure 2.
c = total effect; c' = direct effect

Additional analyses were carried out to test whether other factors moderated the observed mediation effect. In the first analysis, the interaction term gender × conflict was added to the logistic regression model to test whether the effect of conflict with parents on subsequent depression depended on the gender of the child. No moderation by gender effect was detected (interaction term = -0.02, $p = 0.418$), indicating that the effect of conflict with parents on the risk of adolescent depression was similar for boys and girls. Given that depressed mothers tend to have less tolerance for their children's behavior and engage in more conflictual interactions than non-depressed mothers (Goodman & Gotlib, 1999), a second analysis was performed to test whether maternal depression moderated the effect of parent-child conflict on adolescent depression. The interaction effect was not statistically significant (interaction term = 0.02, $p = 0.348$). Conflict with parents remained a significant predictor of adolescent depression (b = 0.04, $p < 0.001$) when taking into account maternal depression.

Is the effect of childhood ADHD on adolescent depression attributable to effects associated with poor academic performance?

The results of the mediation analyses evaluating whether scholastic difficulties at age 11 years accounted for the association between childhood ADHD and adolescent depression are presented in Table 1.6. Childhood ADHD symptoms were predictive of depressive episodes developed between the ages 11 and 17 years ($c = 0.10$, $SE_c = 0.03$, $p < 0.001$) and negatively associated with GPA at age 11 ($a = -0.07$, $SE_a = 0.01$, $p < 0.001$). When accounting for academic performance, ADHD symptoms remained predictive of depression ($c' = 0.09$, $SE_{c'} = 0.03$, $p = 0.002$). GPA was not a statistically significant predictor of depression ($b = -0.15$, $SE_b = 0.13$, $p = 0.255$) when controlling for ADHD symptoms. Gender did not moderate the association between school performance at age 11 and subsequent depression (interaction term = 0.15, $p = 0.539$). The results

did not support the hypothesis that the influence of childhood ADHD on adolescent depression is mediated by poor academic performance.

Does victimization by peers in childhood mediate the relationship between childhood ADHD symptoms and adolescent depression?

The results of the mediation analyses evaluating whether being bullied mediated the association between childhood ADHD and adolescent depression are presented in Table 1.6. Childhood ADHD symptoms were predictive of adolescent depression ($c = 0.09$, $SE_c = 0.02$, $p < 0.001$) and positively associated with being bullied at age 11 ($a = 0.12$, $SE_a = 0.02$, $p < 0.001$). When controlling for victimization by peers, ADHD symptoms still predicted adolescent depression ($c' = 0.09$, $SE_{c'} = 0.02$, $p < 0.001$). There was not a main effect of victimization on the risk of depression ($b = 0.29$, $SE_b = 0.24$, $p = 0.230$), but gender moderated the association between victimization and depression (interaction term = 1.28, $p = 0.008$). Experiencing bullying at age 11 predicted adolescent depression in girls (OR = 2.32, 95% CI = 1.25 – 4.28), but not in boys (OR = 0.65, 95% CI = 0.31 – 1.32).

Given that conduct problems are associated with bullying behavior which may in turn elicit social exclusion and aggression from peers (Coolidge, DenBoer, & Segal, 2004), additional analyses were performed to test whether the effect of childhood victimization on the risk for adolescent depression was moderated by conduct disorder. The interaction effect was not statistically significant (interaction term = -0.01, p =0.980). When controlling for conduct disorder symptoms, childhood victimization remained a significant predictor of adolescent depression in girls (OR = 2.31, 95% CI = 1.25 – 4.27), but not in boys (OR = 0.64, 95% CI = 0.30 – 1.39). In conclusion, the mediation analyses revealed a mediation effect of victimization by peers on depression, moderated by gender. Being bullied in childhood partially mediated the

predictive association between childhood ADHD and adolescent depression in girls, but not in boys.

1.4 DISCUSSION

The current study was undertaken to address the need for prospective longitudinal research examining the risk of depression associated with childhood ADHD, and also potential mechanisms underlying the relationship between ADHD and depression. Specifically, in a population-based longitudinal study spanning three waves of assessment we undertook an investigation of the association between childhood ADHD and adolescent depression developed between the ages 11 and age 17 years in a sample of 998 children and found that:

1. ADHD was a significant contributor to the emergence of adolescent depression in boys as well as girls, and the predictive relationship was robust and not attributable to rater bias effects.
2. ADHD uniquely predicted adolescent depression even when accounting for conduct disorder.
3. ADHD uniquely predicted suicidal ideation, but the association between ADHD and suicide attempts was explained by conduct disorder.
4. Parent-child conflict partially mediated the association between childhood ADHD and adolescent depression.
5. The effect of ADHD on depression was not attributable to demoralization due to poor academic performance.
6. Victimization by peers mediated the relationship between ADHD and depression in girls, but not in boys.

The significance of each of these findings is discussed in turn. Our results indicated that ADHD symptoms uniquely contributed to the emergence of depression in adolescence, even when controlling for conduct disorder symptoms or maternal depression. The predictive relationship between childhood ADHD and adolescent depression was consistent and robust. Teacher ratings of ADHD at 11 years of age also predicted development of depression by 17 years of age, demonstrating that the findings were not due to methodological artifacts attributable to rater bias effects. With regard to gender differences, a non-significant trend was observed whereby the risk of depression conferred by ADHD was higher in girls than in boys. This is not surprising given that by age 11, girls with ADHD show greater deficits in multiple domains than boys with ADHD (Elkins et al., 2011). In addition, ADHD symptoms predicted suicidal ideation through adolescence. In contrast, the association between ADHD symptoms and suicide attempts was explained by conduct disorder.

Our findings did not provide support for the contention that the elevated risk of adolescent depression in children with ADHD is explained by the shared association of each of the disorders with conduct problems. Childhood ADHD symptoms predicted the development of depression by age 17, while controlling for conduct disorder symptoms at baseline. Moreover, childhood ADHD symptoms also predicted the development of depression between 14 and 17 years of age, while controlling for conduct disorder symptoms at age 14 years. This is an important finding, given the substantial growth of conduct problems in adolescence. In contrast, conduct disorder symptoms at age 11 did not predict depression by age 17, nor did conduct symptoms at age 14 predict depression developed between ages 14 and 17 years, when controlling for ADHD symptoms. Our prospective results regarding the lack of predictive value of conduct disorder symptoms when ADHD is taken into consideration pertain to adolescent depression only, and do not exclude the possibility that conduct disorder is associated with elevated risk of adult depression. However, findings from a longitudinal study of a large cohort of

high school students did not support this notion and showed that conduct disorder at age 18 did not predict adult depression by age 30 when controlling for depression at baseline (Olino, Seeley, & Lewinsohn, 2010). Our findings suggest that ADHD needs to be taken into account when examining the developmental impact of conduct problems on the risk for later depression.

Our population-based findings showing that children with ADHD were at higher risk of suicide attempt and suicidal ideation through adolescence are consistent with, and extend previous prospective research involving clinical samples (Biederman, Petty, et al., 2008; Chronis-Tuscano et al., 2010; Hinshaw et al., 2012). The large sample and the substantial proportion of affected girls allowed examination of gender differences with regard to suicide outcomes. We found that while girls were more likely to experience suicidal ideation and attempt suicide, there were no gender differences in the risk of suicidality associated with ADHD. The results that ADHD predicted not only depression, but also the symptom of suicidal ideation, suggest that ADHD may be associated with greater severity of depression.

While previous prospective research in clinically-referred children has shown that conduct disorder symptoms in young children with ADHD predict suicide attempts in adolescence (Chronis-Tuscano et al., 2010), this is the first prospective, community-based study to document that the association between childhood ADHD and suicide attempt in adolescence is accounted by childhood conduct disorder. This finding is significant because we demonstrated that ADHD heightens the risk for depression independent of conduct disorder, but also that the association between childhood ADHD and suicide attempts in adolescence is mediated by conduct disorder, not depression, which carries important clinical implications with respect to screening and prevention efforts. Indirect support for our finding that childhood conduct disorder predicts suicide attempts in adolescence independent of childhood depression and ADHD, is offered by a recent epidemiological study in adults which showed that the progression from suicidal ideation to suicidal behavior is not predicted by depression but by disorders characterized

by poor behavioral control (e.g., conduct disorder) or agitation/anxiety (e.g., post-traumatic stress disorder) (Nock, Hwang, Sampson, & Kessler, 2009).

Our findings indicate that children with ADHD experienced more conflict with their parents than ADHD-free children and that the parent-child conflict at age 11 explained approximately a third of the effect of ADHD on the risk of adolescent depression. These results are consistent with cross-sectional findings showing that parent behavior management mediates the relationship between ADHD and depressive symptoms (Ostrander & Herman, 2006). However, cross-sectional findings do not allow strong inferences as premorbid characteristics present before the onset of depression are confounded with adverse effects of depression and the direction of the effect can be difficult to identify. (For example, depressive symptoms such as irritability may elicit negative parenting behavior leading thus to an association between parenting and child depression.) The current prospective investigation overcomes this methodological limitation and finds that antagonistic parent-child relationships may be a risk factor for adolescent depression in children with ADHD, even when taking maternal depression into consideration. This finding may be explained by the fact that ADHD youth, confronted with significant interpersonal difficulties with peers and struggling academically, may perceive a home environment characterized by criticism, tension and possibly rejection as particularly distressing. Or, perhaps, as proposed by developmental theorists, parenting behaviors contribute to the development of child cognitive styles therefore conflictual parent-child relations may set up the stage for maladaptive, negative cognitive schemas which become more firmly established as the youth encounters social and academic failures, leading to the development of depression (Randolph & Dykman, 1998).

These findings highlight the potential of interventions targeted at improving parent-child relationships for reducing the risk of later depression in children with ADHD. Given that by age 11, the pattern of contentious exchanges with parents is already established, the efforts aimed at

improving parent-child relationships would require early intervention. Prevention and intervention efforts may be targeted at addressing dysfunctional parenting using parent training interventions alone, or in combination with treatment for the youth. Given the social competence deficits associated with ADHD, focus on interpersonal relationships may be fruitful. An intervention that holds promise is Interpersonal Therapy (IPT), which has been shown to be an effective psychosocial intervention for depression (Cuijpers, Geraedts, van Oppen, & Andersson, 2011). Moreover, a recent study showed that an adaptation of the therapy, Interpersonal Therapy - Adolescent Skills Training, developed to be delivered in schools as a preventive intervention for depression, led to considerable reduction of depressive symptoms and also to decrease in mother-child conflict. In addition, the adolescents who experienced high levels of conflict with their mother showed larger improvements in symptoms of depression, consistent with a compensation model of intervention whereby an intervention is most effective for the individuals with the greatest deficits in the areas addressed by the program (Young, Gallop, & Mufson, 2009). IPT needs to be subjected to empirical testing with regard to its effectiveness in ADHD youth and future studies will determine whether adaptations to the therapy are necessary to tailor it for youth with ADHD.

Children with ADHD were found to have considerably lower GPA than ADHD-free children, but the results did not support the hypothesis that scholastic problems mediate the prospective association between childhood ADHD and adolescent depression. The current results are consistent with, and extend prior longitudinal findings with adolescents with ADHD followed through young adulthood (Meinzer et al., 2013). Competency-based models of depression suggest that negative feedback on age-salient developmental tasks such as academic and social performance impact children's self-image and self-esteem and contribute to subsequent depressive symptoms (D. A. Cole, 1990), yet the prospective literature linking academic achievement and depression is sparse and the findings are mixed (Hammen & Rudolph, 2003;

Reinherz et al., 1993). The results of the current study suggest that it is unlikely that poor academic performance is a leading factor depleting the self-esteem of youth with ADHD and forecasting later depression. This proposition is also supported by findings of low self-esteem and elevated rates of depression in intellectually gifted ADHD children (Foley-Nicpon, Rickels, Assouline, & Richards, 2012) and ADHD adults (Antshel et al., 2008). Indirect support for this formulation is also provided by recent findings from a large longitudinal study of a birth cohort which revealed that academic achievement in adolescence is a weak predictor of emotional wellbeing in adulthood, while social competence is a strong predictor (Olsson, McGee, Nada-Raja, & Williams, 2012).

More recent developmental models propose that academic competence and the externalizing and internalizing psychopathology domains are linked by transactional and progressive processes, whereby academic performance and psychopathology domains influence each other over time, in what have been described as cascading effects (Masten et al., 2005). Although developmental cascade models have considerable theoretical appeal and some empirical grounding, the possibility of a confounding effect of "some other cause contributing to both competence and symptoms" is well recognized (Masten, Burt, & Coatsworth, 2006). ADHD fits the profile of such a confounding variable, given its early, stable, and robust associations with academic competence deficits, as well as externalizing and internalizing pathology. Further prospective research is needed to investigate whether the cascade effects linking competence domains and internalizing and externalizing symptoms are attributable to ADHD.

With regard to bullying, our findings indicate that victimization by peers in childhood increases the risk for adolescent depression among ADHD girls but not boys. We also found that the effect was independent of the effects of early conduct problems. To our knowledge, this is the first study to date to examine prospectively the risk of adolescent depression associated with bullying in children with ADHD. The gender specific vulnerability may stem from two sources.

First, compared to boys, girls are more sensitive to the status of their friendships, prioritize connection-oriented goals and are more likely to seek emotional support from their friends (Rose & Rudolph, 2006). Recent prospective findings indicate that among girls, low levels of friends support are a risk factor for depressive symptomatology (Nilsen, Karevold, Røysamb, Gustavson, & Mathiesen, 2013). Also there is evidence to suggest that having friends protects against victimization by peers (Wolke, Woods, & Samara, 2009). Thus, girls may be more sensitive to disruptions to peer relationships, and girls with ADHD may be particularly vulnerable, given that they are socially impaired and have few friends, which increases susceptibility to victimization by peers. Second, peers are less accepting of ADHD-related behaviors when exhibited by girls than by boys, perhaps due to violation of accepted gender norms (Diamantopoulou et al., 2005). This may result in greater levels of social exclusion and neglect among girls with ADHD than boys. Ostracism and the experience of "being left out" is perceived as more aversive by children and adolescents than other bullying behaviors and has a substantial negative impact on self-esteem and perceived self-worth (Saylor et al., 2013). The current study did not distinguish between overt (i.e., physical aggression or threat of physical damage) and relational victimization (i.e., social aggression such as malicious gossip, social neglect or exclusion). While girls with ADHD report elevated rates of both types of victimization (Sciberras et al., 2011), more research is needed to investigate whether relational bullying, and social exclusion in particular, has more detrimental effects than overt bullying. Our finding has important clinical implications regarding the early identification of girls with ADHD at risk for depression and highlights the importance of assessing social functioning of girls with ADHD during clinical encounters.

This study has a number of limitations which will provide impetus for future research. First, the results pertaining to suicidal ideation, particularly the lack of effect of conduct disorder on the risk of suicidal ideation may have been influenced by the restrictive assessment method utilized to evaluate suicidal ideation. Future research is needed to replicate these findings.

Second, in evaluating the risk for depression associated with ADHD, the study did not take into account psychotropic medication for ADHD. The evidence regarding the effect of stimulant medication on the risk of later depression is limited and ambiguous, with some studies finding that psychostimulants protect against depression (Biederman, Monuteaux, Spencer, Wilens, & Faraone, 2009), while others finding no effect (Staikova et al., 2010). If the psychopharmacological interventions for ADHD provide some buffering against depression, then our findings likely underestimate the risk of depression associated with ADHD. Third, our sample was predominantly white, thus the results may not generalize to other racial groups.

To conclude, our results provide important insights with regard to the risk of depression associated with ADHD. More specifically, they show that children with ADHD are at elevated risk for adolescent depression, independent of conduct problems and maternal depression. Moreover, the depression emerging in children with ADHD may be more severe and associated with more suicidal ideation. The present study replicated prior findings linking childhood ADHD and suicide attempts through adolescence but revealed that the association can be accounted for by the presence conduct problems. With regard to potential mechanisms underlying the overlap between ADHD and depression, we found that parent-child conflict in childhood carries substantial risk factor for adolescent depression among children with ADHD, and also that victimization by peers partially mediates the relationship between ADHD and subsequent depression, but only in girls.

Chapter 2 STUDY II

2.1 ABSTRACT

Background. A growing body of evidence indicates that there is substantial comorbidity between ADHD and depression both in adolescents and in adults. However, the etiology of the association between the two disorders remains undetermined. This study aims to investigate the extent of genetic and environmental influences on the covariation between the two phenotypes. **Methods.** The study was conducted in a population-based twin sample enriched with children with disruptive disorders and consisting of 499 twin pairs. ADHD and depression were assessed using structured clinical interviews and parent and child reports. The study utilized biometric modeling. **Results.** Bivariate structural equation modeling revealed that common genetic factors explained the covariance between ADHD and depression. The genetic overlap applied to females, as well as males. **Conclusions**. These findings show that the comorbidity between ADHD and depression is governed by shared genetic factors operating either directly or indirectly via gene-environment correlations or interactions. The results have implications for molecular genetic studies, as well as clinical implications regarding assessment and prevention of depression in at-risk youth.

2.2 INTRODUCTION

Meta-analytic evidence indicates that 12% to 50% of community children and adolescents with ADHD have comorbid depression (Angold et al., 1999). Recent findings from studies involving large, epidemiologically-derived samples, including the first study of this dissertation, confirm elevated risk of depression in youth with ADHD (Chen et al., 2013; Lingineni et al., 2012; Meinzer et al., 2013; Smalley et al., 2007; Sonnby et al., 2011). The comorbidity between ADHD and depression has also been shown in adults, with epidemiological surveys demonstrating that adult ADHD is associated with approximately three-fold increase in odds for depression (Kessler et al., 2006; Zwaan et al., 2011).

When occurring in individuals with ADHD, depression has an earlier age of onset, is associated with more impairment, more intensive treatment histories (Biederman, Ball, et al., 2008; Fishman, Stang, & Hogue, 2007), and greater prevalence of suicidal ideation, as shown in the first study of this dissertation. However, the basis for the association between the two disorders has been underexplored and remains unclear. Overall, these findings indicate that there is a clear need to shed light on the etiology of the overlap between ADHD and depression in order to inform prevention and treatment efforts.

There is strong evidence that ADHD is a highly heritable psychiatric disorder, with a mean heritability estimate of 76% (Faraone et al., 2005). Unlike most other psychiatric disorders, ADHD is uniquely characterized by environmental contributions that appear to consist exclusively of factors that are not shared by twins or siblings (S. A. Burt, 2009). Depression in children and adolescents is also heritable, although the heritability estimates are more modest and show considerable variability across studies (Rice, Harold, & Thapar, 2002b). In contrast with ADHD, the effects of shared environmental influences on depression have been consistently documented in the literature (S. A. Burt, 2009; Silberg, Maes, & Eaves, 2010; Tully, Iacono, &

McGue, 2008). Non-shared environmental influences, including stressful life events, are also instrumental in the etiology of depression, most likely interacting with biological vulnerability (Kendler, Karkowski, & Prescott, 1999).

Findings from family studies suggest that genetic factors may be underlying the comorbidity between ADHD and depression. Depression occurs in first-degree relatives of children with ADHD at a substantially higher rate than chance alone would dictate (Biederman, Faraone, Keenan, & Tsuang, 1991; Chronis et al., 2003; Faraone et al., 2000; Ghanizadeh, Mohammadi, & Moini, 2007; Nigg & Hinshaw, 1998; Segenreich, Fortes, Coutinho, Pastura, & Mattos, 2009). However, family studies do not allow a discrimination between genetic and shared environmental effects, as family resemblance may be due to shared genes or common family environment. Stronger evidence of genetic influences mediating the overlap between ADHD and depression comes from a small adoption study that found increased risk of depression among biological, but not adoptive parents of children with ADHD (Sprich et al., 2000).

Twin designs are well suited for understanding the genetic and environmental factors that contribute to the co-occurrence among disorders, yet to date twin methodology has been used only once to examine the etiologic basis for the phenotypic overlap between ADHD and depression. J. Cole et al. (2009) applied structural equation modeling to parental ratings of 645 child and adolescent twin pairs, aged 5 to 17 years. Bivariate analyses revealed that the covariation between symptoms of ADHD and depression was attributable to substantial shared genetic liability and small to moderate non-shared environmental effects. The study by J. Cole and colleagues (2009) is pioneering, but, nevertheless, its findings are constrained by methodological limitations, including reliance on single rater (parent) and questionnaire measures.

Twin designs are a powerful tool in delineating etiologic factors, and isolate genetic from environmental effects. Nevertheless, issues regarding informant effects remain relevant. It has

been argued that the use of single rater measures of child psychopathology may bias estimates of genetic and environmental effects (Sherman, McGue, & Iacono, 1997). The use of combined information from multiple reporters enhances the accuracy of the clinical description. For example, aggregated child and mother information is a better predictor of teacher report than either child or mother report used alone (S. A. Burt et al., 2001). These results support the use of best-estimate procedures (i.e., combined report from mother and twin) in the assessment of ADHD and depression. Study I of this dissertation provided empirical evidence against the proposition that the association between ADHD and depression reflects an artifact due to maternal rater bias. Moreover, should mothers demonstrate rater bias and inadvertently report higher than objectively warranted psychopathology levels in their children thus leading to spurious phenotypic covariation between ADHD and depression, it is likely that their biased report would affect both twins. Parental over-reporting of child symptoms would result in an overestimate of the shared environmental effects on the covariance between ADHD and depression, an effect which would be particularly manifest in studies relying solely on parental report. However, the findings from the J. Cole et al. (2009) study, indicating a lack of shared environmental effects on the co-occurrence between ADHD and depression, are not consistent with the notion that rater bias effects emanating from parental depression bias the estimates of genetic and environmental contributions to the covariation between the two disorders.

In the present study, we address the gap in the literature by investigating the etiology of the comorbidity between ADHD and depression in a population based sample of adolescent twins, using biometric modeling to investigate the etiologic basis of the co-occurrence between ADHD and depression. The genetic and environmental contributions to the covariation between the two disorders were examined in two ways. First, we computed the correlations between genetic, shared and non-shared variance components of each of the disorders. The magnitude of these correlations reflects the extent to which the genetic, shared, and non-shared environmental

effects on depression and ADHD are the same or different. For instance, a large genetic correlation would suggest that the genetic factors influencing one disorder are to a great extent the same genetic factors responsible for the other disorder. Second, we computed the proportion of the observed phenotypic covariance between the disorders that could be traced to genetic, shared and non-shared environmental influences.

The present study has several advantages worth noting: cohort sample with participants at similar developmental stage, reliance on structured clinical interview measures, use of aggregate measures incorporating child and parent ratings, prospective measurement of disorders thus minimizing recall errors, and lifetime assessment of depression, which is an important consideration given the episodic nature of the disorder.

2.3 METHOD

2.3.1 Participants

Participants were the 11-year-old twins participating in the Enrichment Study (ES), an extension of the Minnesota Twin and Family Study (MTFS), designed to yield a genetically-informative sample at risk for the development of substance abuse and augmented with children likely to be diagnosed with ADHD and conduct disorder. The sample consisted of 520 females and 478 males and was ascertained from Minnesota birth records of 2717 like-sex twin pairs born between 1988 and 1994. Of these, 82% were successfully located and their families were contacted to participate in the study in the year the twins became 11 years old. Seventy-six percent of the families were randomly assigned to be screened by phone for parent-reported symptoms of ADHD, conduct disorder and related behaviors. The screened families were invited to participate if at least one member of the twin pair met or exceeded a symptom threshold from a list of DSM symptoms of ADHD, conduct disorder, as well as indications of academic disengagement. The

symptom threshold was determined using data from the 11-year old cohort from the MTFS and was calculated to enhance the probability of selecting twins having a diagnosis of ADHD or conduct disorder. The rest of the located families were recruited to the study without prior screening. Additional eligibility requirements for participating families included living within driving distance from the University of Minnesota Twin Cities campus and neither twin having an intellectual or physical impairment that interfered with their ability to complete the intake visit. Seventy-six percent of the eligible families completed the intake assessments, and of these, 48% were from the screened sample. Mean age was 11.9 for both boys (SD= 0.41) and girls (SD= 0.44). Ninety-one percent of the sample was Caucasian, representative of the children born in Minnesota in the birth years sampled (see Keyes et al. (2009) for more details on sample recruitment strategy and sample characteristics). Zygosity was determined based on three estimates: parental ratings of twin physical similarity as reported on a zygosity questionnaire, staff evaluation of the twins' physical similarity, and twin similarity obtained from an algorithm using fingerprint ridge count and cephalic and ponderal indices. When the zygosity estimates were inconsistent, a serological analysis was performed. The sample consisted of 300 monozygotic (MZ) twins and 199 dizygotic (DZ) twins. The ES sample is being followed every three years, with the first and second follow-ups concluded.

2.3.2 Measures

After being provided a description of the study, participants gave written consent or assent, as appropriate. At every assessment, each parent and each member of the twin pair was interviewed separately by a different interviewer who held a B. A. or M. A. in psychology and underwent extensive training. The clinical interviewers assessed symptoms of mental health disorders according to the DSM-IV criteria. The reporting period at intake was lifetime, and since the

previous assessment at each of the follow-ups. At intake and first follow-up (age 14), maternal and self-reports of each twin's symptoms of ADHD and major depressive disorder were obtained using a modified version of the Diagnostic Interview for Children and Adolescents – Revised (DICA-R) (Reich, 2000; Welner, 1987). At second follow-up (age 17), twins underwent assessment for depression using the Structured Clinical Interview for DSM-IV; mothers reported on the twins' symptoms of ADHD and depression using the parent version of the DICA-R. Symptoms were counted toward a diagnosis if endorsed by either child or primary caretaker, using a best-estimate procedure, which provides better validity than using either rater alone (S. A. Burt et al., 2001). Diagnoses were made at two levels of certainty: definite and probable. At the definite level, a diagnosis was assigned if all the necessary criteria were met; at the probable level, all necessary symptom criteria were present with the exception of one symptom. This assessment method was used to minimize the likelihood of false negative diagnoses and prevent underreporting in community sample and when assessing lifetime psychopathology (Iacono et al., 1999). The diagnoses obtained have good reliability with kappas exceeding .74.

At intake, 25.6% of the sample was diagnosed with ADHD, 144 boys and 111 girls. The proportion of males to females diagnosed with ADHD in this sample does not reflect the general prevalence of the disorder but rather the recruitment strategy of the study. For this study, we utilized the lifetime ADHD symptom count and the lifetime depression diagnosis both at age-17 follow-up. Compared to diagnoses, symptom counts provide a more sensitive index of the underlying construct and afford greater statistical power (MacCallum, Zhang, Preacher, & Rucker, 2002). The ADHD symptom count variable was computed by summing up all the ADHD symptoms that were endorsed by either mother or twin at any of the assessments (intake, age-14 follow-up, age-17 follow-up). Given that all the participants had ADHD data at intake, this operational definition of lifetime ADHD symptoms resulted in no missing data on lifetime ADHD symptoms. Several factors permitted this operational definition of lifetime symptoms of

ADHD. First, ADHD has a very early age of onset, with 95% of all lifetime ADHD beginning by age 11 (Kessler et al., 2005). Second, unlike most common mental disorders, ADHD shows an overall declining symptom trajectory from childhood to late adolescence. Third, the study had a low attrition rate.

Due to the study's assessment procedures whereby symptoms of depression were not administered and recorded unless the participant endorsed at least two weeks of anhedonia or depressed mood, the depression symptom count variable was not suitable for these analyses given that it did not reflect the distribution of depressive symptoms in the population. Therefore the depression diagnosis variable was used instead. Participants received a lifetime depression diagnosis at age 17 if they fulfilled the criteria for depression at either intake, or age-14 follow-up or age-17 follow-up assessments. Of the 998 individual twins in the base sample, 902 twins (90.4%) had lifetime depression data at age 17. To determine whether loss at follow-up resulted in a biased sample it was tested whether sex or diagnoses of ADHD or depression affected the likelihood of participation at follow-up assessments, using generalized estimating equations for logistic regression to account for the relatedness of the participants. Attrition analyses indicated that boys and girls did not differ significantly in rate of participation at first ($\chi^2(1) = 0.19, p = 0.664$) or second ($\chi^2(1) = 0.23, p = 0.634$) follow-up. Among boys, a diagnosis of ADHD at intake did not significantly influence the likelihood of participation at the first ($\chi^2(1) = 0.01, p = 0.904$) or second ($\chi^2(1) = 0.07, p = 0.786$) follow-up. A diagnosis of major depressive disorder at intake did not significantly influence the likelihood of participation at the first ($\chi^2(1) = 0.53, p = 0.465$) or second ($\chi^2(1) = 1.31, p = 0.253$) follow-up. Among girls, a diagnosis of ADHD at intake did not significantly influence the likelihood of participation at the first ($\chi^2(1) = 1.29, p = 0.255$) or second ($\chi^2(1) = 0.28, p = 0.597$) follow-up. Also, a diagnosis of major depressive disorder at intake did not significantly influence the likelihood of

participation at the first ($\chi^2(1) = 0.19, p = 0.659$) or second ($\chi^2(1) = 0.24, p = 0.621$) follow-up.

2.3.3 Statistical Analyses

Twin methodology makes use of the similarity between monozygotic (MZ) and dizygotic (DZ) twins to decompose the phenotypic variance of a trait into three or four components: additive genetic effects (A), dominant genetic effects (D), shared environmental effects (C), and non-shared environmental effects (E). Non-shared environmental effects also include measurement error. Given that MZ twins share all their genes, and DZ twins share on average 50% of their segregating genes, the correlation between additive genetic effects is 1.0 in MZ twins and 0.5 in DZ twins, while the correlation between dominance effects is 1.0 for MZ twins and 0.25 for DZ twins. Twin similarity arises not only from shared genes but also from shared environment, which is the component of the environment that is common between the twins and renders the twins more similar to each other. In twins reared together, the correlation between shared environmental effects is 1.0 for both MZ and DZ twins. Non-shared environmental factors consist of environmental influences unique to each individual within the twin pair, acting to make the twins less similar, therefore the non-shared environmental effects are uncorrelated for twins, regardless of their zygosity. In twins reared together shared environmental influences and dominance genetic effects cannot be estimated simultaneously as the data does not contain enough information to tease apart C from D thus one of the two parameters (C or D) must be set to 0. If data on adoptive siblings is available then the simultaneous estimation of both components is feasible, as the adoptive siblings provide an estimate of the shared environmental effects (Rijsdijk & Sham, 2002).

Structural equation modeling can be employed to model the MZ and DZ correlations to estimate genetic and environmental underlying the variance or covariance of traits. In the current study, structural equation models were fit to the raw data using OpenMx for R (Boker et al., 2011). Participants with incomplete data were included in the analyses to fully utilize all available information from the dataset. Maximum likelihood estimates were computed in the presence of missing data using the full information maximum likelihood (FIML) method. The maximum likelihood estimation is an iterative method involving repeated attempts to obtain estimates of parameters that yield the smallest possible discrepancies between the model and the observed data. Sampling weights were incorporated in the likelihood function to account for the study's recruitment strategy and oversampling of children with disruptive disorders. The sampling weighs were computed as the inverse of the probability of selection into the ES sample, thus lower weights were assigned to the screened twin pairs and higher weights to the unscreened twin pairs in order to obtain parameter estimates that apply to the general population. Estimation in structured equation modeling using maximum likelihood assumes normality of continuous outcomes. As it is typical in a population-based sample, the symptom count lifetime ADHD variable was not normal (skew = 0.47; kurtosis = 0.16), although the departure from normality was slight (i.e., absolute values of skewness and kurtosis less than 1) and slight non-normality has little effect on standard errors or parameter estimates, particularly in relatively large samples as the one used here (Yuan, Bentler, & Zhang, 2005). No transformation was therefore undertaken and raw ADHD scores were used in all the analyses. Effects of age at age-17 follow-up were regressed out on the observed scores.

A preliminary investigation of the sources of variation within and across disorders was conducted by computing twin correlations for each measure by zygosity and gender. Comparisons of MZ and DZ correlations provide initial estimates of genetic and environmental effects underlying each of the traits, as well as their covariation. Phenotypic correlations (within-

person cross-trait) and cross-twin correlations were obtained by fitting a saturated model which did not impose any biometric constraints. To identify the model, the mean of the latent variable underlying the depression diagnosis was fixed to 0 and the standard deviation to 1. The estimation of correlations was followed by biometric analysis of the twin data.

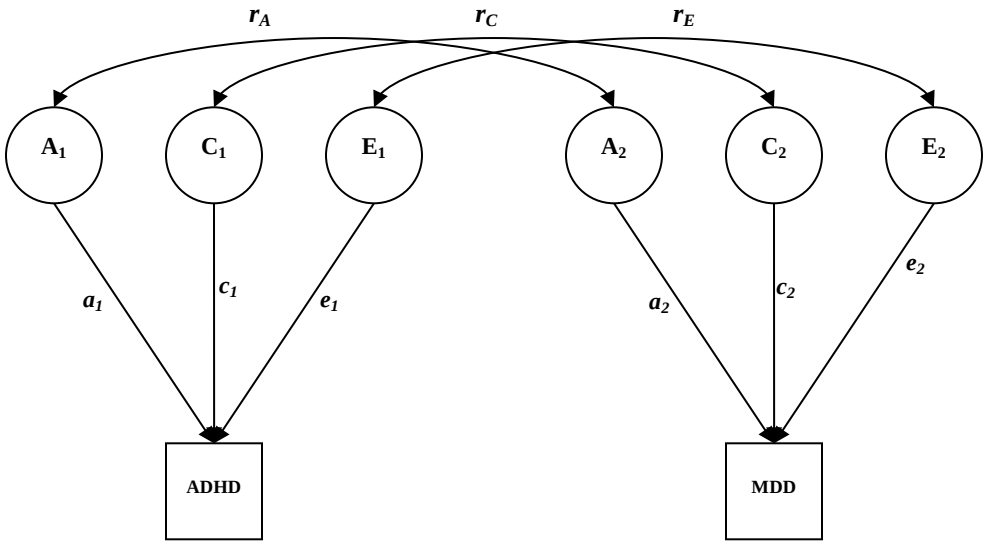

Figure 2.1 Correlated factors model. r_A, r_C, r_E = genetic, shared environmental and non-shared environmental correlations.

The focus of the present study was to understand the extent to which common factors (genetic or environmental) underlie the association between ADHD and depression, thus a correlated factors solution was interpreted, which is mathematically equivalent to the Cholesky solution (Loehlin, 1996). The correlated factors model allows the estimation of the extent to which the same genes or environmental factors underlie the covariation between the traits examined. As depicted in Figure 2.1, the variance for each of the traits is partitioned into genetic and environmental influences, and the correlations between the components are estimated. In the correlated factors solution, the paths from the A, C, and E factors are the square root of the

heritability (a^2), and the shared (c^2) and unique (e^2) environmentalities underlying each variable. The genetic correlation, denoted here by r_A, reflects the extent to which the same genetic factors influence both traits. The genetic correlation is not dependent on the heritability of the traits, such that two traits, each with low heritability, can nonetheless be highly correlated genetically. Based on the genetic correlation and the heritability of each trait, the proportion of the phenotypic correlation that is due to shared genetic factors, called bivariate heritability, can be estimated: $\frac{a_1 r_A a_2}{a_1 r_A a_2 + c_1 r_C c_2 + e_1 r_E e_2}$, where r_C and r_E are the shared and unique environmental factors correlations, and $a_1 r_A a_2 + c_1 r_C c_2 + e_1 r_E e_2$ is the phenotypic correlation between the two measured variables. The proportions due to shared and non-shared environmentalities can be computed in the same fashion.

The comparative fit of candidate models was evaluated using the index of model fit Akaike Information Criterion (AIC), corrected for sample size. AIC provides an estimate of the relative distance between the fitted model and the unknown, true process that generated the observed data. The AIC is computed: $AIC = -2\ln(L) + 2k$, where L is the maximized value of the likelihood function for the estimated model and k is the number of parameters in the model (Akaike, 1987). Given the penalty for number of estimated parameters, it follows that AIC rewards both goodness of fit and model parsimony. The preferred model of a set of candidate models is the one with the lowest AIC value. Compared to other goodness of fit indices such as the likelihood ratio test (the chi-square difference test), the AIC has the advantage of being valid for comparison of non-nested models (Burnham & Anderson, 2002). When the number of parameters to be estimated is large in relation to the sample size, the sample size corrected AIC (AICc) is used (Hurvich & Tsai, 1989). $AICc = AIC + \frac{2k(k+1)}{n-k-1}$, where n is the sample size and k is the number of parameters in the model. It has been argued that AICc should be used regardless of sample size, as AICc tends to AIC with large sample sizes (Burnham & Anderson, 2002).

The confidence intervals for parameter estimates were obtained using bias corrected percentile bootstrapping. The bootstrap method is a computationally intensive procedure for making statistical inferences that uses resampling techniques to generate an empirical estimate of a statistic's sampling distribution (Efron & Tibshirani, 1993). By treating the observed original sample as the population, and drawing repeated subsamples from this pseudo-population, bootstrapping simulates replication. Thus, it allows assessment of the accuracy of a parameter estimate given that the mean of its values across bootstrap re-samples approximates the true value of the parameter. The nonparametric bootstrap technique was utilized as no assumptions about the underlying distributions were made.

2.4 RESULTS

Descriptive statistics for lifetime ADHD symptoms and lifetime depression diagnosis at age 17 are presented in Table 2.1. The cumulative lifetime prevalence of depression at age 17 was 25.3%, which is higher than epidemiological rates reported in participants of comparable age (Hamdi & Iacono, 2013; Merikangas et al., 2010), in part due to prospective ascertainment which substantially increases lifetime prevalence rates compared to retrospective assessment (Moffitt et al., 2009). The computation of the lifetime ADHD symptom count variable did not take into account duration requirements or exclusionary rules at any of the assessments, thus the rates reflect upper estimates of ADHD prevalence. As expected, adolescent girls had higher lifetime prevalence of depression than adolescent boys ($\chi^2(1) = 8.67, p = 0.003$) and fewer lifetime ADHD symptoms ($t(996) = 6.84$, $p < 0.001$).

Table 2.1 Summary statistics of lifetime ADHD symptoms and lifetime depression diagnosis, both at age 17.

	Males			Females			Total		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
ADHD Symptoms	478	7.64	4.94	520	5.48	5.01	998	6.51	5.09
	N	Frequency	%	N	Frequency	%	N	Frequency	%
Depression Diagnosis	432	90	20.8	470	138	29.4	902	228	25.3

Correlations between ADHD and depression were computed to provide preliminary estimation of the magnitude of phenotypic covariation and the genetic and environmental influences on the disorders and their covariation. Table 2.2 contains the within-twin and cross-twin correlations for ADHD and depression. Elements in the first column contain the within-twin cross-trait correlations. These correlations characterize the phenotypic relationship between ADHD and depression and therefore should be similar across zygosity. The magnitude of these correlations provides evidence of moderate phenotypic covariation between ADHD and depression. Elements in the second and third columns of Table 2.2 contain the cross-twin within-trait correlations, computed for each zygosity. The MZ and DZ cross-twin correlations for ADHD, and those for depression, respectively, were compared to obtain a preliminary indication of the degree to which genetic and environmental factors influenced each of the disorders. The pattern of cross-twin correlations for ADHD was similar in males and females. The MZ correlations were lower than 1, indicating that person specific environmental effects influence the variance of the trait. The DZ correlations were lower than half the MZ correlations, suggesting large heritable effects and the possibility of non-additive (dominance) genetic effects. With regard to depression, the MZ correlations were less than unity, indicating non-shared environmental influences, and the DZ correlations were larger than half the MZ correlations, suggestive of heritable influences and the possibility of shared environmental effects.

The cross-twin cross-trait correlations, given in the last column of Table 2.2, provide a preliminary indication of the sources (genetic and/or environmental) of covariance between ADHD symptoms and depression. When comparing the cross-twin cross-trait correlations for females, the DZ correlations were lower than the MZ correlations suggesting that heritable and environmental effects influence the covariance of the two disorders. For males, the DZ correlations were similar in magnitude to the MZ correlations suggesting shared environmental influences on the phenotypic correlation. The somewhat lower MZ correlations for ADHD and depression in the males compared to the females, together with the sex difference in the pattern of cross-twin cross-trait correlations, suggest the possibility of gender differences in heritable influences, a possibility tested formally using biometric methods.

Table 2.2 Twin correlations (standard errors) for ADHD and depression by gender and zygosity.

	Within-Twin Cross-Trait	Cross-Twin Depression	Cross-Twin ADHD	Cross-Twin Cross-Trait
Females				
MZ	0.38 (0.07)	0.74 (0.09)	0.80 (0.03)	0.36 (0.08)
DZ	0.43 (0.09)	0.51 (0.17)	0.21 (0.10)	0.26 (0.10)
Males				
MZ	0.38 (0.08)	0.62 (0.12)	0.74 (0.04)	0.32 (0.08)
DZ	0.37 (0.10)	0.56 (0.19)	0.28 (0.10)	0.32 (0.11)

All correlations statistically significant at $p < 0.05$.

Table 2.3 Comparative fit indexes for biometric models

Bivariate Model	-2LL	k	AICc	ΔAICc
ACE				
Sex variant	5980.01	21	6023.95	10.18
Sex invariant	6005.62	12	6030.26	16.49
ADE				
Sex variant	5977.26	21	6021.19	7.42
Sex invariant	6003.34	12	6027.98	14.21
AE				
Sex variant*	5982.78	15	6013.77	0
Sex invariant	6007.89	9	6026.25	12.48
AE-ACE				
Sex variant	5981.17	17	6016.45	2.68
Sex invariant	6006.52	10	6026.97	13.2

-2LL = log likelihood fit statistic; k = number of parameters estimated; AICc = Akaike Information Criterion corrected for sample size; ΔAICc = difference in AICc between the model with the lowest AICc (sex variant AE) and each of the other models; Sex-variant model = parameters were allowed to differ between sexes; Sex-invariant = parameters were not allowed to differ. AE-ACE models: C factor fixed to 0 for ADHD.
*Preferred model

In order to better summarize the correlation patterns evident in Table 2.2, explicit statistical models were fitted. Based on prior research implicating genetic dominance effects in the genetic etiology of ADHD symptoms (Nikolas & Burt, 2010) and given the pattern of cross-twin correlations for ADHD, models including dominance effects were also tested. The fit indexes of the bivariate models fitted are shown in Table 2.3. In the sex-variant models the parameters were free to differ between males and females, whereas in the sex-invariant models the parameters were constrained to be equal between sexes. As it is evident in Table 2.3, when the models were evaluated using the comparative index of fit AICc, the models that allowed the parameters to differ between sexes fit better than the sex-invariant models. The AE with sex differentiation model was the best fitting model, obtaining the lowest AICc value. This indicates that the AE model with sex differences achieved the best balance between fit and parsimony given the observed data.

Figure 2.2 shows the standardized parameter estimates and the 95% confidence intervals for the sex-variant AE model. Even though the AE model that allowed for sex differences fit better than the sex-invariant AE model, the standardized parameter estimates were of similar magnitude for males and females. As indicated elsewhere (McGue, Iacono, & Krueger, 2006), this suggests that the primary source of the significant sex effect is the difference in variance between the sexes (males: $variance_{ADHD} = 22.25$, $variance_{depression} = 2.80$; females: $variance_{ADHD} = 20.66$, $variance_{depression} = 4.04$).

Paths coefficients in the Figure 2.2 need to be squared to determine the proportion of variance contributed by a specific path. The parameters are standardized thus the sum of squared paths pointing at a variable sum to 1. The genetic and environmental factors underlying ADHD symptoms and depression respectively, and the proportion of the covariance explained by genetic and environmental factors are reported in Table 2.4. The proportion of the total variance in ADHD due to additive genetic influences was high for both males (72.9%) and females (80.7%). The remaining variance in ADHD (27.1% for males and 19.3% for females) was explained by non-shared environmental influences. The heritability estimates for depression were 64.3% for males and 75.3% for females, with the remainder of the variance explained by non-shared environmental influences. As illustrated in Figure 2.2, the genetic correlation was statistically significant for both males and females and of substantial in magnitude ($r_A = 0.49$ for both males and females). The correlations between non-shared environmental influences were very low, 0.04 for males and 0.02 for females and their confidence intervals included 0. As shown in Table 2.4, the bivariate heritability for males was 96.7% for males and 98.8% for females, indicating that the phenotypic overlap between ADHD and depression can be attributed almost entirely to shared genetic factors.

Table 2.4 Proportion of variance and proportion of covariance due to genetic and environmental factors.

	Proportion of variance accounted for by:		Proportion of covariance between ADHD symptoms and depression explained by:	
Disorder	A	E	A	E
Males			96.7*	3.3
ADHD	72.9*	27.1*		
MDD	64.3*	35.7*		
Females			98.8*	1.2
ADHD	80.7*	19.3*		
MDD	75.3*	24.7*		

Estimates from the sex-variant AE model. A and E represent additive genetic and non-shared environmental influences. * $p < 0.05$.

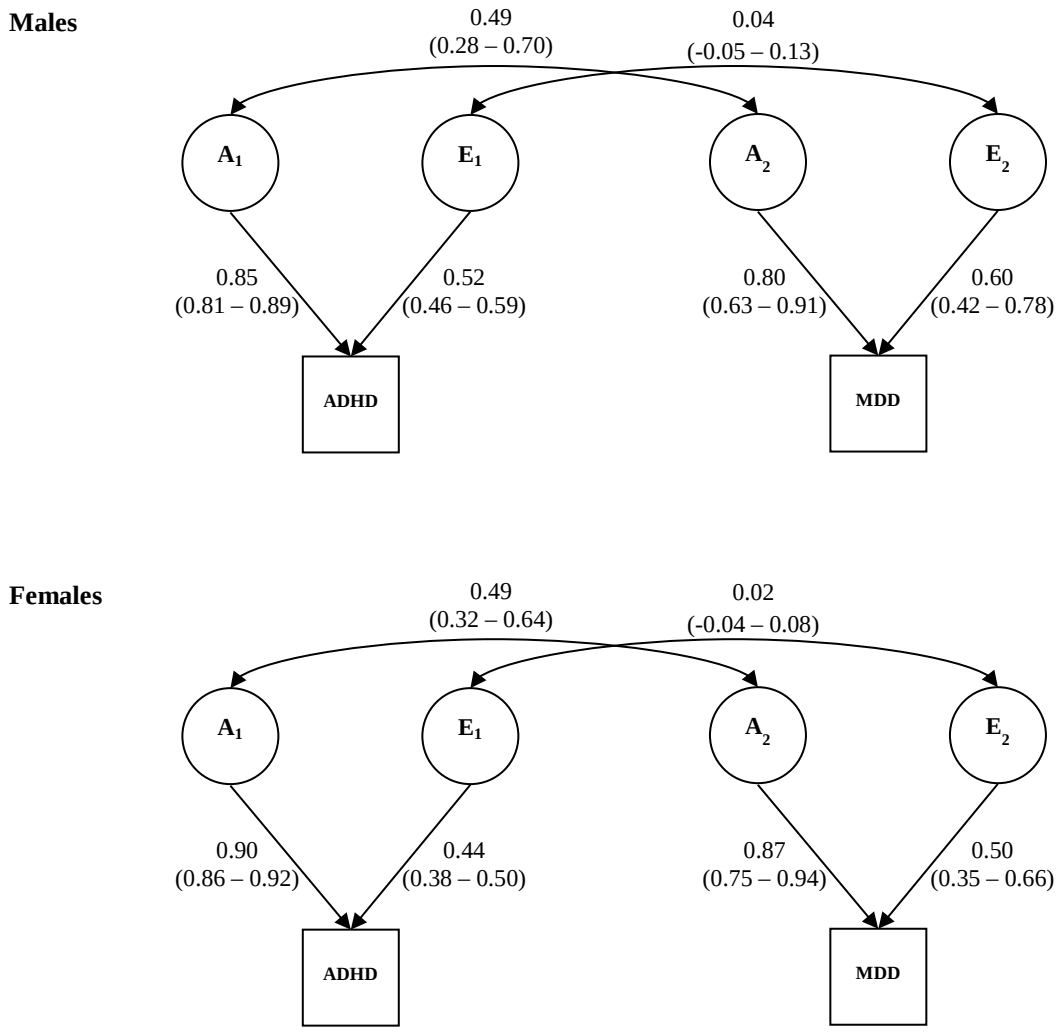

Figure 2.2 Correlated factors solution for the sex-variant AE model. The curved arrows represent correlations between the latent factors. Coefficients in the diagram are standardized, and the 95% confidence intervals are presented in parentheses.

2.5 DISCUSSION

The purpose of this study was to examine the etiologic basis of the phenotypic link between ADHD and depression in adolescence. More specifically, the study sought to determine the extent to which genetic and environmental factors are responsible for the covariation between the two disorders. Using robust assessment methods in a twin cohort sample, the current study provides evidence of shared genetic etiology between ADHD symptoms and depression. Model-fitting

indicated that the association between the two disorders is governed by genetic factors. Only one prior twin study (J. Cole et al., 2009) investigated genetic and environmental contributions to the association between ADHD and depression using different data-collection and assessment strategies (e.g., mailed questionnaires) in a sample of children and adolescents recruited from a different geographical area (Wales, UK). Yet, the current findings are largely consistent with those reported by J. Cole et al. (2009). Indeed, the current study estimated that the proportion of the phenotypic overlap between ADHD and depression accounted for by shared genetic effects was 97% for males and 99% for females; J. Cole et al. (2009) estimated that the proportion of phenotypic covariation explained by common genetic influences was 76% for boys and 84% for girls, with the remaining variance explained by environmental influences that make the twins different from one another. Unlike J. Cole and colleagues (2009) who detected small to moderate non-shared environmental contributions, we did not find that non-shared environmental influences exerted an effect on the covariation between the two pathologies. The dissimilar findings may be related to the fact that the current sample is on average older (mean age = 17.9) than the one utilized by J. Cole et al. (2009) (mean age = 10.6). The age discrepancy is relevant because of age related changes in heritability of the two phenotypes. While the heritability of ADHD seems to remain unchanged from childhood to adolescence (Nikolas & Burt, 2010), the heritability of depression appears to increase and environmental influences to decline (Rice, Harold, & Thapar, 2002a).

Model fitting did not support a shared environmental contribution to the overlap between ADHD and depression, although the cross-twin cross-trait correlations hinted at c^2 effects in males. While by most standards our sample is not small, the dichotomous operationalization of depression reduced the statistical power (MacCallum et al., 2002), therefore it is plausible that there was limited power to resolve more than one source of familial risk. Consequently, small shared environmental effects on the covariance between ADHD and depression cannot be ruled

out for males. However, in order for common environmental experiences to influence the association between two traits, shared environmental effects need to play a role in the etiology of each of the two phenotypes. Yet, meta-analytic evidence on ADHD indicates that similarity between twins appears to be due entirely to genetic factors, with no apparent contributions from common environment (S. A. Burt, 2009). Additionally, while shared environmental contributions have been documented in studies of child and adolescent depression, their magnitude is lower when the disorder is assessed via diagnostic interview, as in the current study, with a meta-analytic estimate of c^2 of 0.05 and not significantly different than 0 (S. A. Burt, 2009).

It is important to underscore that our finding regarding the lack of environmental influences applies strictly to the covariation between ADHD and depression, and not to the individual phenotypes. Model-fitting showed that non-shared environmental effects of moderate magnitude contributed to the etiology of each of the disorders. The finding of shared genetic liability to the comorbidity between ADHD and depression does not exclude a role for environment influences. If there are gene–environment correlations or interactions, in a standard ACE model their effect is incorporated into the genetic term therefore they would not have been identified by the models tested here. In view of the finding that the comorbidity between ADHD and depression is governed by the same set of genes, two main possibilities emerge with regard to the etiological mechanisms underlying the overlap between the two pathologies. First, it is possible that ADHD increases exposure to environmental hazards that predispose to depression, consistent with a gene-environment correlation model. This notion is supported by findings from the first study of this dissertation, which showed that conflict with parents and, for girls only, victimization by peers mediated the association between childhood ADHD and adolescent depression. Second, ADHD and depression may represent varied manifestations of the same genetic liability emerging at different stages of development. Investigations using endophenotypes based on neuropsychology and neuroimagining may be fruitful. A potential

endophenotype with theoretical appeal is emotion regulation, which has been associated with both ADHD and depression (Barkley, 2010; Durbin & Shafir, 2008). Deficits in emotion regulation appear to precede the onset of depression (Feng et al., 2009) and recent evidence suggests that emotion regulation abnormalities mediate the association between ADHD and depression in preadolescent children (Seymour et al., 2011). Another plausible marker associated with both disorders involves abnormalities in neural circuitry supporting working memory (Mannie, Harmer, Cowen, & Norbury, 2010; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005).

The fact that the genetic liabilities for ADHD and depression overlap, at least for the comorbid pattern of the disorders, has implications for molecular genetic studies. A profitable strategy would be to explore genes associated with one disorder in the other condition. The results of the current study also have clinical implications. Given that ADHD and depression have non-overlapping risk periods, the presence of shared genetic influences underscores the need for screening and assessment instruments that are sensitive to the detection of comorbidity. The finding that the covariation between ADHD and depression is governed by genes bears limited association with the treatability of these conditions. In fact, since the age of onset for ADHD is in the early school years while depression does not typically emerge until adolescence or later, in the adult years (Kessler et al., 2005), this offers a window of opportunity for prevention and intervention efforts.

The results of the current study should be interpreted in the context of several limitations. First, while our use of composite assessment measures minimized the issue of shared method variance, it is possible that because mothers rated both twins on ADHD and depression, this would make the twins appear more similar, resulting in an overestimate of the shared environmental effects. However, the present findings indicating a lack of shared environmental influences do not support this notion. Second, due to the sample size and the categorical

operationalization of depression, the present study may not have had sufficient power to detect shared environmental contributions to depression. Larger studies may provide additional insights regarding the influence of shared environment. Third, some features of the current data seemed to be poorly captured by the best-fitting biometric model. Specifically, male cross-twin cross-trait correlations suggest shared environmental contributions and weaker genetic effects than the estimates from the bivariate biometric model. While this discrepancy can be an expression of imprecision in estimation associated with lower power, it may also signal that alternative formulations may warrant consideration. Fourth, we utilized a standard Cholesky model transformed to a correlated factors solution to estimate genetic and environmental effects. Future studies will benefit from testing the presence of gene-environment correlation or interaction effects. Fifth, the study involved a homogeneous, primarily Caucasian sample residing in Minnesota, thus results may not generalize to other racial or ethnic groups.

Chapter 3 CONCLUDING REMARKS

A growing body of research has documented that childhood ADHD is associated with elevated risk of depression in adolescence. Moreover, youth with ADHD are more likely to experience suicidal ideation and attempt suicide than their ADHD-free counterparts. However, there is a dearth of studies investigating the underpinnings of the association between ADHD and depression thus our knowledge about its etiology is remarkably limited. Concerns regarding whether the relationship between the two disorders reflects a true psychological phenomenon or rather a spurious association attributable to rater bias effects or conduct disorder further obscure the origin of the relationship. To date, the relevant literature has been dominated by studies involving predominantly male, clinically ascertained samples which constrains generalizability and precludes examination of gender differences. Furthermore, although studies using traditional family designs have uncovered a familial link between ADHD and depression, genetically informative studies are necessary to reveal the etiology of the relationship.

The present work sought to address this critical gap in the literature by first, submitting the association between childhood ADHD and adolescent depression to rigorous empirical scrutiny to exclude the possibility that the relationship is artifactual, and second, by shedding light on its etiology. Two studies were undertaken in a population-based cohort twin sample (520 girls and 478 boys) enriched with children with disruptive disorders, followed from 11 years to 17 years of age. The first study examined the prospective relationship between ADHD at age 11 and depression developed between age 11 years and 17 years, while accounting for rater bias effects and the influence of conduct disorder. The association between ADHD and suicidal ideation and behavior was also examined. Additionally, the study assessed the potential mediating roles of conflict with parents, academic underperformance, and victimization by peers in the association between childhood ADHD and adolescent depression. The second study estimated the magnitude

of the genetic and environmental contributions to the overlap between childhood ADHD and adolescent depression using a twin design.

Collectively, the studies yielded four primary findings. First, symptoms of ADHD at age 11 years were a significant predictor of depression developed between the ages 11 years and 17 years, and the association between childhood ADHD and subsequent depression was consistent and robust. A non-significant trend hinted that the risk of depression conferred by ADHD was higher in girls than in boys. Two convergent results strongly suggested that the relationship between ADHD and depression was not attributable to rater bias effects. ADHD symptoms predicted the emergence of depression in adolescence, even when taking into account lifetime maternal depression. Also, teacher ratings of ADHD at age 11 predicted adolescent depression. The fact that the findings were similar when using different reporters of children's ADHD symptoms, as exhibited in dissimilar settings (school and home), strengthens our confidence that the association between childhood ADHD and adolescent depression is a genuine finding, and not an artifactual effect due to depressed mothers overstating their children's symptoms. Moreover, the results showed that childhood ADHD symptoms predicted adolescent depression even when controlling for conduct problems, suggesting that the relationship between ADHD and depression is robust and not a spurious statistical result stemming from the comorbidity of each of the disorders with conduct disorder.

Second, the association between ADHD and subsequent depression appeared to be governed by genetic influences, consistent with the only other twin study to date that examined the etiology of the association between ADHD and mood symptoms using twin methodology in a genetically informative sample (J. Cole et al., 2009). We found that environmental influences exerted negligible effects on the covariation between the two disorders. However, these results do not exclude a role for environmental influences in the form of gene-environment correlations or gene-environment interactions.

Third, childhood ADHD was associated with risk of experiencing suicidal ideation through age 17 years. Given that in this sample, the majority of the youth endorsing suicidal ideation were also depressed, the results suggest that ADHD may be associated with greater severity of depression, consistent with reports from clinical studies (Biederman, Ball, et al., 2008). While childhood ADHD symptoms also predicted suicide attempts through age 17, the association was explained by conduct disorder. This result extends findings from adult studies (Nock et al., 2009), suggesting that in adolescence aggressive tendencies are linked with elevated risk to self.

Fourth, antagonistic relations with parents, and for girls only, victimization by peers partly mediated the association between ADHD and adolescent depression. These findings suggest an evocative gene-environment correlation mechanism. In other words, the results are consistent with the notion that the genetic endowment of the child with ADHD elicits stressful environmental conditions which in turn contribute to the development of depression. Thus, the etiology of the relationship between childhood ADHD and adolescent depression is primarily genetic but the mediation pathway is at least in part environmental.

Implications

The findings of the present studies strongly indicate that childhood ADHD is a predictor of adolescent depression and that genetic influences underlie the association between ADHD and depression. The current findings are timely. The recent DSM 5 re-classification of ADHD as a neurodevelopmental disorder, and the updated criteria designed to more accurately characterize the experience of adults with the disorder, mark critical changes in the conceptualization of ADHD. Not only is the disorder more enduring than previously thought, but as the current findings indicate, it has a broader impact on psychological functioning, beyond the extensively

researched associations with externalizing spectrum disorders. Taken together, the present findings have several important ramifications.

1. The present results carry clinical implications. Incorporating depression screening as part of the clinical care of youth with ADHD would be an important step toward early identification of youth at risk for depression, and implementation of proactive intervention. Also, it would not be premature to test early prevention interventions targeting parenting skills, alone, or alongside child-focused interventions designed to promote development of social skills.
2. The present findings call into question the accepted notion that conduct disorder is a risk factor for adolescent depression by showing that the link between conduct problems and depression is driven by ADHD. Therefore, a re-evaluation of the relationship between conduct disorder and adolescent depression in the context of ADHD may be warranted.
3. Common mental disorders are currently conceptualized in terms of two broad internalizing and externalizing spectra (Krueger & Markon, 2006). The current findings suggest that the two spectra may be less distinct than previously conceptualized and that the neurodevelopmental deficits encompassed by ADHD may contribute to explain the substantial comorbidity between disorders of the externalizing and internalizing spectra.
4. Developmental models posit that internalizing and externalizing propensities and academic and social competence are linked by transactional and progressive processes over time (Masten et al., 2006). The present findings suggests that models hypothesizing a dynamic interplay over time between domains of competence and psychopathology may require further empirical scrutiny by taking into account ADHD's associations with both psychopathology domains, as well as academic and social functioning. This would shed additional light on the processes underpinning the development and maintenance of psychopathology in childhood and adolescence.

Next Steps

The above findings show that childhood ADHD is associated with adolescent depression and shed light on the etiology of the co-occurrence, but more research is needed to further characterize the association between the two disorders and to more fully elucidate the mechanisms underlying it. Future longitudinal studies with follow-up periods extending into adulthood should clarify whether ADHD is associated with greater risk of depression in females compared to males, and also whether ADHD represents a liability for depression with onset in adulthood. The current findings suggest that depression occurring in individuals with a childhood history of ADHD may be of greater severity than depression in ADHD-free youth. Longitudinal studies using alternative indices of severity (e.g., history of treatment, psychiatric hospitalizations) are needed to further substantiate this finding. The current findings indicate that the association between ADHD and depression is governed by shared genetic factors. Future molecular genetic research capitalizing on findings from both ADHD and depression studies may provide additional insights into the etiology of the association between ADHD and depression. Investigations using endophenotypes based on neuropsychology and neuroimagining may be fruitful. Preliminary evidence suggests that emotion regulation (Seymour et al., 2011), hedonic responsivity (Meinzer, Pettit, Leventhal, & Hill, 2012), abnormalities in neural circuitry supporting working memory (Mannie et al., 2010; Martinussen et al., 2005) may be suitable endophenotype candidates.

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